

## ABO blood type, long-standing diabetes, and the risk of pancreatic cancer

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blood type O. Compared with the non-DM group, the DM group had a higher frequency of blood type B [odds ratio (OR) = 2.61, 95%CI: 1.24-5.47; reference group: blood type A]. Moreover, male (OR = 3.17, 95%CI: 1.67-6.06), older than 70 years of age (OR = 2.19, 95%CI: 1.20-3.98) and presence of a family history of diabetes (OR = 6.21, 95%CI: 3.38-11.36) were associated with long-standing type 2 diabetes. The mean ages were  $64.8 \pm 9.2$  years,  $67.1 \pm 9.8$  years, and  $71.7 \pm 7.0$  years in the subgroups with the duration of diabetes, 3-5 years, 5.1-14.9 years, and 15 years or more, respectively ( $P = 0.007$ ). A comparison of ABO blood type distribution among the subgroups also showed a significant difference ( $P = 0.03$ ).

**CONCLUSION:** The association of pancreatic cancer with blood type and duration of diabetes needs to be further examined in prospective studies.

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**Key words:** Pancreatic cancer; ABO blood type; Diabetes mellitus; Risk factor; Screening

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### Abstract

**AIM:** To retrospectively study pancreatic cancer patients with respect to their ABO blood type and diabetes.

**METHODS:** Our analysis included a cohort of 1017 patients with pancreatic ductal cancer diagnosed at our hospital in Tokyo. They were divided into two groups: 114 patients with long-standing type 2 diabetes (DM group, defined as diabetes lasting for at least three years before the diagnosis of pancreatic cancer) and 903 patients without diabetes (non-DM group). Multivariate analysis was performed to identify factors that are associated with long-standing diabetes. The DM group was further divided into three subgroups according to the duration of diabetes (3-5 years, 5.1-14.9 years, and 15 years or more) and univariate analyses were performed.

**RESULTS:** Of the 883 pancreatic cancer patients with serologically assessed ABO blood type, 217 (24.6%) had

### INTRODUCTION

Pancreatic cancer is the fifth leading cause of cancer deaths in Japan, accounting for approximately 26000 deaths each year<sup>[1]</sup>. Because of the poor prognosis, identifying high-risk individuals and the modifying risk factors are important strategies for preventing pancreatic cancer. Despite intensive research efforts, the etiology of spo-

radic pancreatic cancer remains largely unknown. Epidemiologic studies have consistently shown that smoking and long-standing type 2 diabetes are two modifiable risk factors for pancreatic cancer<sup>[2,3]</sup>. The association between diabetes and pancreatic cancer is complex because diabetes and pancreatic cancer development may involve a similar pathogenesis and share common risk factors, such as obesity, smoking and insulin resistance. Moreover, although long-standing type 2 diabetes is a risk factor for pancreatic cancer, new-onset diabetes may also result from pancreatic cancer<sup>[4,5]</sup>. There is a lack of data on the proportion of pancreatic cancer cases that can be attributed to long-standing diabetes and the prevalence of pancreatic cancer-induced new-onset diabetes.

In addition, although an association between the ABO blood type and various diseases was proposed 50 years ago<sup>[6,7]</sup>, the ABO blood type has recently been confirmed to be associated with malignant tumors, including skin cancer<sup>[8]</sup>, esophageal cancer<sup>[9]</sup>, hepatocellular carcinoma<sup>[10]</sup> and pancreatic cancer<sup>[11-16]</sup>. Regarding pancreatic cancer risk, both epidemiologic<sup>[11-15]</sup> and genome-wide association studies (GWAS)<sup>[16]</sup> showed that individuals carrying the O blood type had the lowest risk compared with those with non-O blood types.

Although diabetic patients may represent a high-risk group for pancreatic cancer, the increasing prevalence of type 2 diabetes in the general population and the lack of specific biomarkers do not justify screening all diabetic patients for the early detection of pancreatic cancer. It is possible that among diabetic patients, a subset of diabetics who are at high risk of developing pancreatic cancer may show different characteristics from other diabetics, including the duration of diabetes and blood type distribution. In this study, we retrospectively examined 1017 patients with pancreatic cancer, focusing on the duration of type 2 diabetes and the ABO blood type.

## MATERIALS AND METHODS

### Patients

We reviewed the medical records of patients with pancreatic ductal cancer diagnosed between 1975 and 2009 at Tokyo Metropolitan Komagome Hospital. A total of 1022 patients were included in the present analysis. Overall, 66.3% had histological confirmation, and the remaining patients were diagnosed based on either endoscopic retrograde cholangiopancreatography or at least two imaging modalities. To exclude the possibility that new-onset diabetes was caused by pancreatic cancer, we defined individuals with long-standing diabetes as those who had diabetes for at least 3 years before the diagnosis of pancreatic cancer. Among the 1022 patients, we excluded 5 patients with long-standing diabetes due to diagnoses other than type 2 diabetes.

The subjects were divided into two groups: 114 patients with long-standing type 2 diabetes (DM group) and 903 patients without long-standing type 2 diabetes (non-DM group). Furthermore, we classified the DM group into 3 subgroups according to the duration of

preexisting diabetes: a relatively short period of 3-5 years (DM-S group: 31 patients), a medium range of 5.1-14.9 years (DM-M group: 48 patients), and a relatively long period of 15 years or more (DM-L group: 35 patients). Information on gender, age, smoking status, ABO blood type, diabetes, a family history of diabetes and tumor location was recorded from medical charts. The ABO blood type was assessed serologically, and the information of DM was primarily based on self-report. For 92 patients in the DM group, their medical history revealed the type of medical treatment that they had received for diabetes.

This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital.

### Statistical analysis

First, age, gender, smoking status (never *vs* former or current), a family history of diabetes (present *vs* absent in a first-degree relative), the location of the cancer (head *vs* body or tail) and the ABO blood type were compared using univariate analysis. A two-sample *t*-test was conducted with age as a continuous variable. A  $\chi^2$  test was used for categorical variables. The unconditional logistic regression method was used to compare the DM group with the non-DM group using variables that showed a *P* value of less than 0.15 in the univariate analyses. Variables for which the *P* value exceeded 0.05 were eliminated in a stepwise fashion such that only those that had a statistically significant association with long-standing type 2 diabetes were included in the final regression model. In this analysis, blood type A was used as a reference group. The final models were evaluated for goodness-of-fit with the Hosmer-Lemeshow test.

Similar to the analyses mentioned above, we performed univariate analyses among 3 subgroups of the DM group. A one-way analysis of variance was conducted for continuous variables, and a  $\chi^2$  test was used for categorical variables.

We used the  $\chi^2$  test to compare the ABO blood type distribution in our pancreatic cancer patients with the distribution reported from a nationally representative sample of the Japanese population<sup>[17]</sup>.

All of the *P* values were two-sided, with statistical significance set at *P* < 0.05. All of the statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences) 19 statistical package software (IBM Japan, Tokyo).

## RESULTS

Table 1 shows the characteristics of the DM group and the non-DM group and the results of univariate analyses and multivariate analysis. The sex ratio (male/female) was significantly higher in the DM group than in the non-DM group (*P* = 0.002). The mean age of the DM group was 1.8 years older at the diagnosis of pancreatic cancer than the non-DM group ( $67.9 \pm 9.2$  years *vs*  $66.1 \pm 10.6$  years, *P* = 0.08). In accordance with this result, there were more patients older than 70 years of age

**Table 1** Characteristics of the diabetes mellitus group and the non-diabetes mellitus group *n* (%)

Variables	DM group ( <i>n</i> = 114)	Non-DM group ( <i>n</i> = 903)	<i>P</i> value	OR (95%CI)
Sex			0.002	
Female	33 (28.9)	398 (44.1)		Reference
Male	81 (71.1)	505 (55.9)		3.17 (1.67-6.06)
Age (yr)			0.009	
< 70	53 (46.5)	541 (59.9)		Reference
≥ 70	61 (53.5)	362 (40.1)		2.19 (1.20-3.98)
Smoking status	<i>n</i> = 99 <sup>1</sup>	<i>n</i> = 715	0.28	
Former and current smokers	60 (60.6)	392 (54.8)		
Non-smokers	39 (39.4)	323 (45.2)		
Tumor location			0.37	
Head	58 (50.9)	501 (55.5)		
Body/tail	56 (49.1)	402 (44.5)		
Family history of DM	<i>n</i> = 76	<i>n</i> = 393	< 0.001	
No	41 (53.9)	335 (85.2)		Reference
Yes	35 (46.1)	58 (14.8)		6.21 (3.38-11.36)
ABO blood type	<i>n</i> = 104	<i>n</i> = 779	0.06	
A	35 (33.7)	338 (43.4)		Reference
B	28 (26.9)	175 (22.5)		2.61 (1.24-5.47)
O	34 (32.7)	183 (23.5)		1.92 (0.95-3.87)
AB	7 (6.7)	83 (10.7)		0.94 (0.28-3.14)

<sup>1</sup>Because of missing data, the numbers of subjects are presented for smoking status, family history of diabetes, and ABO blood type in each group. Diabetes mellitus (DM) group represents pancreatic cancer patients with long-standing type 2 diabetes, defined as diabetes lasting at 3 years prior to the diagnosis of pancreas cancer. Non-DM group represents pancreatic cancer patients without long-standing type 2 diabetes. OR: Odds ratio determined by the logistic regression method.

in the DM group than the non-DM group ( $P = 0.009$ ). Subjects in the DM group were more likely to have a family history of diabetes than those in the non-DM group ( $P < 0.001$ ). The distribution of the ABO blood type seemed to differ between the DM group and non-DM group ( $P = 0.06$ ). There were no significant differences in the smoking status ( $P = 0.28$ ) or tumor locations ( $P = 0.37$ ) between the two groups.

The logistic regression method using candidate variables resulting from the univariate analyses revealed that sex, age, a family history of diabetes and ABO blood type were associated with long-standing type 2 diabetes. Interestingly, the frequency of blood type B was significantly higher in the DM group than in the non-DM group (Table 1). The Hosmer-Lemeshow test showed that the regression model had an acceptable goodness-of-fit ( $P > 0.05$ ).

There were no significant differences in gender, smoking status, a family history of diabetes or the location of cancer among the 3 subgroups defined by the duration of diabetes. However, significant differences in age ( $P = 0.007$ ) and the ABO blood type ( $P = 0.03$ ) were observed among the 3 subgroups (Table 2). We found a significant difference in the ABO blood type distribution between our pancreatic cancer patients and the general Japanese population<sup>[17]</sup> ( $P = 0.02$ ). As shown in Table 3, our patients had a lower frequency of blood type O and a higher frequency of blood type A.

**Table 2** Comparison of characteristics among 3 diabetes mellitus subgroups according to duration of diabetes

Variables	DM-S ( <i>n</i> = 31)	DM-M ( <i>n</i> = 48)	DM-L ( <i>n</i> = 35)	<i>P</i> value
Sex ratio (M/F)	2.44	2.69	2.18	0.91
Age, yr (mean ± SD)	64.8 ± 9.2	67.1 ± 9.8	71.7 ± 7.0	0.007
≥ 70	41.9%	47.9%	71.4%	0.03
Smoking status	<i>n</i> = 26 <sup>1</sup>	<i>n</i> = 43	<i>n</i> = 30	0.12
Former and current smokers	50.0%	72.1%	53.3%	
Tumor location: Head	54.8%	47.9%	51.4%	0.83
Family history of DM	<i>n</i> = 16	<i>n</i> = 36	<i>n</i> = 24	0.64
Positive family history of DM	56.3%	44.4%	41.7%	
ABO blood type	<i>n</i> = 26	<i>n</i> = 44	<i>n</i> = 34	0.03
A	19.2%	52.3%	20.6%	
B	26.9%	18.2%	38.2%	
O	42.3%	27.3%	32.4%	
AB	11.5%	2.3%	8.8%	

<sup>1</sup>Because of missing data, the numbers of subjects are presented for smoking status, family history of diabetes and ABO blood type in each group. F: Female; M: Male; DM: Diabetes mellitus; DM-S: Patients with diabetes of 3-5 years; DM-M: Patients with diabetes of 5.1-14.9 years; DM-L: Patients with diabetes of 15 years or more.

**Table 3** Comparison of the distribution of ABO blood type between our cases and the general Japanese population *n* (%)

ABO blood type	Our pancreatic cancer patients ( <i>n</i> = 883)	General Japanese population ( <i>n</i> = 4465349) <sup>1</sup>
A	373 (42.2)	1725950 (38.7)
B	203 (23.0)	988996 (22.2)
O	217 (24.6)	1305924 (29.3)
AB	90 (10.2)	444479 (10.0)

<sup>1</sup>The data was referred to Fujitas' article<sup>[17]</sup>.

## DISCUSSION

In our retrospective examination of 1017 pancreatic cancer patients, we found that the distribution of the ABO blood type in our cases is different from that of the general Japanese population. Furthermore, the distribution of the blood type also seemed to differ between the DM group and the non-DM group, with the DM group having a higher frequency of blood type B. This finding suggests that long-standing type 2 diabetes and other underlying factors that are associated with diabetes, such as blood type, might play a role in predisposing diabetic patients to pancreatic cancer.

Because of the increasing prevalence of type 2 diabetes in the general population and the absence of specific biomarkers, it is not cost-effective to screen for pancreatic cancer in asymptomatic diabetics. Therefore, it is important to identify a subset of diabetics with a higher susceptibility to pancreatic cancer than other diabetics. We addressed this issue by focusing on the duration of diabetes and the ABO blood type.

It remains unclear whether the duration of diabetes significantly predicts pancreatic cancer risk. Previous studies have noted an inverse association between the duration of diabetes and the pancreatic cancer risk; the

association appeared to be strongest among individuals with a duration of diabetes less than 4 years, with a relative risk of 2.1 (95%CI: 1.9-2.3)<sup>[3]</sup>. However, in a large Korean cohort study, the pancreatic cancer risk was significantly increased with an increasing duration of diabetes in men: the hazard ratios were 2.0, 2.4 and 3.0 for individuals with a duration of diabetes less than 4.9 years, 5.0-9.9 years, and 10 years or more, respectively<sup>[18]</sup>. Despite the inverse association observed in a meta-analysis published in 2005, individuals with long-standing diabetes (> 5 years) were still at a 50% increased risk of pancreatic cancer<sup>[3]</sup>. Interestingly, when we divided the DM group into 3 subgroups according to the duration of diabetes, we found that among long-standing diabetes-related pancreatic cancer cases, there may be several subgroups that are associated with a specific blood type and characterized by the period from the onset of diabetes to the occurrence of pancreatic cancer. This finding suggests that patients with long-standing type 2 diabetes might not be considered a single uniform group.

Regarding the ABO blood type, several lines of evidence in recent years have shown that the ABO blood type is associated with a risk of pancreatic cancer. A prospective cohort study noted an elevated risk of incidental pancreatic cancer among subjects with blood type A, AB or B compared with blood type O, and those with blood type B had the highest risk<sup>[11]</sup>. In addition, they also reported increased risk with the addition of each non-O allele<sup>[12]</sup>. A recent GWAS, which mainly involved Caucasian populations, identified an association between a single-nucleotide polymorphism (SNP) in the ABO gene locus (rs505922) and pancreatic cancer<sup>[16]</sup>. Accordingly, an article by Nakao and co-workers, which is the only study on pancreatic cancer and the ABO blood type alleles in Japanese subjects, showed that the risk of pancreatic cancer was higher among those with the non-O blood type than those with the O blood type<sup>[14]</sup>. The distribution of the ABO blood type in our overall pancreatic cancer patients was similar to that reported in the Nakao's article. In fact, when the ABO blood type distribution in our pancreatic cancer patients was compared with their cases<sup>[14]</sup>, univariate analysis with the chi-square test showed no difference between them ( $P = 0.56$ ). Moreover, considering that the frequency of the O blood type in our patients was lower than that observed in the general Japanese population, our study provided indirect evidence that the O blood type may be associated with a lower risk of pancreatic cancer in Japanese people.

Another interesting finding is that the B blood type is more common in pancreatic cancer patients with long-standing type 2 diabetes than in those without diabetes. The association between the ABO blood type and diabetes is controversial. Advances in genome-wide sequencing have provided novel insights into the pathogenesis of diabetes mellitus. A recent GWAS showed that genetic variants in the ABO locus were associated with not only diabetes risk, with blood group B showing a decreased risk compared with blood group O<sup>[19]</sup>, but also the plasma levels of soluble intercellular adhesion molecule 1 and

soluble E selectin<sup>[19-22]</sup>, both of which are markers of inflammation and are thought to be related to the risk of type 2 diabetes mellitus<sup>[23,24]</sup>. In addition, a SNP at the ABO locus was reported to be strongly associated with serum tumor necrosis factor alpha<sup>[25]</sup>, which is a pro-inflammatory cytokine that modulates rates of pancreatic ductal cell apoptosis<sup>[26]</sup>, and an adipocytokine that has been implicated in the development of insulin resistance<sup>[27]</sup>. Although the mechanism underlying the association between ABO blood type, diabetes and pancreatic cancer has not been clarified, these findings suggest interactions among ABO blood types, inflammatory markers, type 2 diabetes and pancreatic cancer.

A major strength of this study is a large cohort of pancreatic cancer patients. Our study has several limitations. First, the major limitation is the lack of an appropriate control group comprising long-standing type 2 diabetes patients without pancreatic cancer. Although our finding showed that the B blood type is more common among pancreatic cancer patients with long-standing type 2 diabetes, a prospective cohort study of diabetics is warranted to confirm whether long-term diabetics with the B blood type have an increased risk of pancreatic cancer. Second, because the study subjects were selected from one hospital, the generalization of our results to other populations is unclear. As mentioned above, with regard to the distribution of the ABO blood type, pancreatic cancer cases in Nakao's study were comparable to ours. Thus, our subjects are not particularly unique. Third, the history of diabetes was mainly based on self-reporting, and the accuracy of the self-reported information is unknown. However, because it is unlikely that a patient would be forgetful regarding the minimum duration of 3 years, a self-report that the duration was 3 years or more than 3 years was likely to be reliable. Fourth, we cannot exclude the possibility that the significant differences observed in ABO blood types among the 3 subgroups were due to chance because of the small number of subjects in each subgroup. This issue warrants further examination in a larger population.

In summary, the retrospective examination of a large cohort of pancreatic cancer patients showed that the B blood type is more common in pancreatic cancer patients with long-standing type 2 diabetes than in those without diabetes. Further studies are needed to better define the set of factors associated with an increased susceptibility to pancreatic cancer in diabetic patients.

## COMMENTS

### Background

Pancreatic cancer is a dismal disease and refractory to almost all current therapies. Because of the poor prognosis, identifying high-risk individuals and modifying risk factors are important strategies for preventing pancreatic cancer. Currently, smoking habits and type 2 diabetes are well-known modifiable risk factors for pancreatic cancer. However, the prevalence of smoking and the increasing incidence of type 2 diabetes in the general population do not justify screening all subjects for the early detection of pancreatic cancer.

### Research frontiers

Recently, there has been emerging evidence that the ABO blood type is associ-

ated with pancreatic cancer risk. A prospective cohort study noted an elevated risk of incidental pancreatic cancer among subjects with blood type A, AB or B compared with blood type O, and those with blood type B had the highest risk.

### Innovations and breakthroughs

In their retrospective examination of a large cohort of pancreatic cancer patients, authors found that the distribution of the ABO blood type seemed to differ between patients with long-standing type 2 diabetes and those without, with the former showing a higher frequency of blood type B. In addition, when they divided the former group into 3 subgroups according to the duration of diabetes, they found that there may be several subgroups associated with a specific blood type and characterized by the duration of diabetes. These findings suggest that long-standing type 2 diabetes and other underlying factors, such as blood type and period of diabetes, may play a role in predisposing diabetic patients to pancreatic cancer.

### Applications

Although their results should be replicated in prospective studies, they may be useful to define a subset of diabetics that is associated with increased susceptibility to pancreatic cancer.

### Terminology

Long-standing type 2 diabetes: Type 2 diabetes represents a complex interaction between hereditary conditions and environmental factors and is essentially different from diabetes secondary to pancreatic cancer. Long-standing diabetes here is defined as diabetes for at least 3 years prior to the diagnosis of pancreatic cancer. This duration should be sufficient to rule out diabetes secondary to the tumor due to the rapid fatal course of pancreatic cancer.

### Peer review

Nice retrospective study that is well supported by advanced statistical methodology. Extremely well written in idiomatic English, and limitations are appropriately described. All in all, a good study with marginal clinical relevance.

## REFERENCES

- WHO Mortality Database. Available from: URL: <http://www.who.int/healthinfo/morttables/en/index.html>
- Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008; **393**: 535-545 [PMID: 18193270 DOI: 10.1007/s00423-007-0266-2]
- Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; **92**: 2076-2083 [PMID: 15886696 DOI: 10.1038/sj.bjc.6602619]
- Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, Petersen GM. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology* 2008; **134**: 95-101 [PMID: 18061176 DOI: 10.1053/j.gastro.2007.10.040]
- Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* 2009; **10**: 88-95 [PMID: 19111249 DOI: 10.1016/S1470-2045(08)70337-1]
- Roberts JA. Blood groups and susceptibility to disease: a review. *Br J Prev Soc Med* 1957; **11**: 107-125 [PMID: 13471902]
- Moniwa H. Statistical studies on the correlation between the ABO-blood groups and some diseases. *Tohoku J Exp Med* 1960; **72**: 275-289 [PMID: 13772037 DOI: 10.1620/tjem.72.275]
- Xie J, Qureshi AA, Li Y, Han J. ABO blood group and incidence of skin cancer. *PLoS One* 2010; **5**: e11972 [PMID: 20694147 DOI: 10.1371/journal.pone.0011972]
- Caygill CP, Royston C, Charlett A, Wall CM, Gatenby PA, Ramus JR, Watson A, Winslet M, Hourigan CS, Dev Bardhan K, Barrett's, blood groups and progression to oesophageal cancer: is nitric oxide the link? *Eur J Gastroenterol Hepatol* 2011; **23**: 801-806 [PMID: 21701391 DOI: 10.1097/MEG.0b013e3283489d9c]
- Li Q, Yu CH, Yu JH, Liu L, Xie SS, Li WW, Yang X, Fan WB, Gai ZT, Chen SJ, Kato N. ABO blood group and the risk of hepatocellular carcinoma: a case-control study in patients with chronic hepatitis B. *PLoS One* 2012; **7**: e29928 [PMID: 22235351 DOI: 10.1371/journal.pone.0029928]
- Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, Giovannucci EL, Fuchs CS. ABO blood group and the risk of pancreatic cancer. *J Natl Cancer Inst* 2009; **101**: 424-431 [PMID: 19276450 DOI: 10.1093/dnci/djp020]
- Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, Stolzenberg-Solomon RZ, Arslan AA, Jacobs EJ, Lacroix A, Petersen G, Zheng W, Albanes D, Allen NE, Amundadottir L, Anderson G, Boutron-Ruault MC, Buring JE, Canzian F, Chanock SJ, Clipp S, Gaziano JM, Giovannucci EL, Hallmans G, Hankinson SE, Hoover RN, Hunter DJ, Hutchinson A, Jacobs K, Kooperberg C, Lynch SM, Mendelsohn JB, Michaud DS, Overvad K, Patel AV, Rajkovic A, Sánchez MJ, Shu XO, Slimani N, Thomas G, Tobias GS, Trichopoulos D, Vineis P, Virtamo J, Wactawski-Wende J, Yu K, Zeleniuch-Jacquotte A, Hartge P, Fuchs CS. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. *Cancer Res* 2010; **70**: 1015-1023 [PMID: 20103627 DOI: 10.1158/0008-5472.CAN-09-2993]
- Greer JB, Yazer MH, Raval JS, Barmada MM, Brand RE, Whitcomb DC. Significant association between ABO blood group and pancreatic cancer. *World J Gastroenterol* 2010; **16**: 5588-5591 [PMID: 21105191 DOI: 10.3748/wjg.v16.i44.5588]
- Nakao M, Matsuo K, Hosono S, Ogata S, Ito H, Watanabe M, Mizuno N, Iida S, Sato S, Yatabe Y, Yamao K, Ueda R, Tajima K, Tanaka H. ABO blood group alleles and the risk of pancreatic cancer in a Japanese population. *Cancer Sci* 2011; **102**: 1076-1080 [PMID: 21306478 DOI: 10.1111/j.1349-7006.2011.01907x]
- Ben Q, Wang K, Yuan Y, Li Z. Pancreatic cancer incidence and outcome in relation to ABO blood groups among Han Chinese patients: a case-control study. *Int J Cancer* 2011; **128**: 1179-1186 [PMID: 20473916 DOI: 10.1002/ijc.25426]
- Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Jacobs EJ, LaCroix A, Zheng W, Albanes D, Bamlet W, Berg CD, Berrino F, Bingham S, Buring JE, Bracci PM, Canzian F, Clavel-Chapelon F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Fox JW Jr, Gallinger S, Gaziano JM, Giovannucci EL, Goggins M, González CA, Hallmans G, Hankinson SE, Hassan M, Holly EA, Hunter DJ, Hutchinson A, Jackson R, Jacobs KB, Jenab M, Kaaks R, Klein AP, Kooperberg C, Kurtz RC, Li D, Lynch SM, Mandelson M, McWilliams RR, Mendelsohn JB, Michaud DS, Olson SH, Overvad K, Patel AV, Peeters PH, Rajkovic A, Riboli E, Risch HA, Shu XO, Thomas G, Tobias GS, Trichopoulos D, Van Den Eeden SK, Virtamo J, Wactawski-Wende J, Wolpin BM, Yu H, Yu K, Zeleniuch-Jacquotte A, Chanock SJ, Hartge P, Hoover RN. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet* 2009; **41**: 986-990 [PMID: 19648918 DOI: 10.1038/ng.429]
- Fujita Y, Tanimura M, Tanaka K. The distribution of the ABO blood groups in Japan. *Jinrui Idengaku Zasshi* 1978; **23**: 63-109 [PMID: 691841 DOI: 10.1007/BF02001790]
- Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; **293**: 194-202 [PMID: 15644546 DOI: 10.1001/jama.293.2.194]
- Qi L, Cornelis MC, Kraft P, Jensen M, van Dam RM, Sun Q, Girman CJ, Laurie CC, Mirel DB, Hunter DJ, Rimm E, Hu FB. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. *Hum Mol Genet* 2010; **19**: 1856-1862 [PMID: 20147318 DOI: 10.1093/hmg/ddq057]
- Paré G, Chasman DI, Kellogg M, Zee RY, Rifai N, Badola S, Miletich JP, Ridker PM. Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women. *PLoS Genet* 2008; **4**: e1000118 [PMID: 18604267 DOI: 10.1371/journal.pgen.

- 1000118]
- 21 **Paterson AD**, Lopes-Virella MF, Waggott D, Boright AP, Hosseini SM, Carter RE, Shen E, Mirea L, Bharaj B, Sun L, Bull SB, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Genome-wide association identifies the ABO blood group as a major locus associated with serum levels of soluble E-selectin. *Arterioscler Thromb Vasc Biol* 2009; **29**: 1958-1967 [PMID: 19729612 DOI: 10.1161/ATVBAHA.109.192971]
- 22 **Barbalic M**, Dupuis J, Dehghan A, Bis JC, Hoogeveen RC, Schnabel RB, Nambi V, Bretler M, Smith NL, Peters A, Lu C, Tracy RP, Aleksic N, Heeriga J, Keaney JF Jr, Rice K, Lip GY, Vasani RS, Glazer NL, Larson MG, Uitterlinden AG, Yamamoto J, Durda P, Haritunians T, Psaty BM, Boerwinkle E, Hofman A, Koenig W, Jenny NS, Witteman JC, Ballantyne C, Benjamin EJ. Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. *Hum Mol Genet* 2010; **19**: 1863-1872 [PMID: 20167578 DOI: 10.1093/hmg/ddq061]
- 23 **Meigs JB**, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. *JAMA* 2004; **291**: 1978-1986 [PMID: 15113816 DOI: 10.1001/jama.291.16.1978]
- 24 **Song Y**, Manson JE, Tinker L, Rifai N, Cook NR, Hu FB, Hotamisligil GS, Ridker PM, Rodriguez BL, Margolis KL, Oberman A, Liu S. Circulating levels of endothelial adhesion molecules and risk of diabetes in an ethnically diverse cohort of women. *Diabetes* 2007; **56**: 1898-1904 [PMID: 17389327 DOI: 10.2337/db07-0250]
- 25 **Melzer D**, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, Lauretani F, Murray A, Gibbs JR, Paolisso G, Rafiq S, Simon-Sanchez J, Lango H, Scholz S, Weedon MN, Arepalli S, Rice N, Washecka N, Hurst A, Britton A, Henley W, van de Leemput J, Li R, Newman AB, Tranah G, Harris T, Panicker V, Dayan C, Bennett A, McCarthy MI, Ruukonen A, Jarvelin MR, Guralnik J, Bandinelli S, Frayling TM, Singleton A, Ferrucci L. A genome-wide association study identifies protein quantitative trait loci (pQTLs). *PLoS Genet* 2008; **4**: e1000072 [PMID: 18464913 DOI: 10.1371/journal.pgen.1000072]
- 26 **Garcea G**, Dennison AR, Steward WP, Berry DP. Role of inflammation in pancreatic carcinogenesis and the implications for future therapy. *Pancreatology* 2005; **5**: 514-529 [PMID: 16110250 DOI: 10.1159/000087493]
- 27 **Mishima Y**, Kuyama A, Tada A, Takahashi K, Ishioka T, Kitabata M. Relationship between serum tumor necrosis factor-alpha and insulin resistance in obese men with Type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2001; **52**: 119-123 [PMID: 11311966 DOI: 10.1016/S0168-8277(00)00247-3]

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