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Relationship between ABO blood group alleles and pancreatic cancer is modulated by secretor (FUT2) genotype, but not Lewis antigen (FUT3) genotype

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Abstract

Background: In western populations, Pancreatic Ductal Adenocarcinoma (PDAC) risk has been found to be greater among individuals with non-O blood types than those with O blood type. However, the association has not been fully evaluated with respect to *FUT2* (determining secretor status) and *FUT3* (determining Lewis antigens) status, two biologically important genes in the expression of ABO blood groups with PDAC.

Methods: We examined interactions in data from 8,027 cases and 11,362 controls in large pancreatic cancer consortia (PanScan I-III and PanC4) by using genetic variants to predict ABO blood groups (rs505922 and rs8176746), secretor status (rs601338), and Lewis antigens

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(rs812936, rs28362459, and rs3894326). Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of the risk of PDAC adjusted for age and sex. We examined multiplicative interactions of ABO with secretor status and Lewis antigens by considering each product term between ABO and secretor and between ABO and Lewis antigens individually.

Results: We found that the increased risk associated with non-O blood groups was somewhat stronger among secretors than non-secretors (ORs 1.28 [95% CI: 1.15–1.42] and 1.17 [95% CI: 1.03–1.32] respectively; interaction p-value = 0.002). We did not find any interactions between ABO and Lewis antigens.

Conclusions: Our large consortia data provide evidence of effect modification in the association between non-O blood type and pancreatic cancer risk by secretor status.

Impact: Our results indicate that the association between ABO blood type and PDAC risk may vary by secretor status, but not by Lewis antigens.

Keywords

pancreatic adenocarcinoma; *ABO* blood alleles; secretor (*FUT2*); Lewis antigen (*FUT3*)

Introduction

Pancreatic cancer, of which 95% of cases are pancreatic adenocarcinoma (PDAC), is the third leading cause of cancer-related death and the second most commonly diagnosed gastrointestinal cancer in the United States with a 5-year survival rate of ~ 11% (1). Established epidemiologic risk factors include tobacco smoking, obesity, diabetes, and a family history of pancreatic cancer (2). ABO blood group has been implicated in the risk of pancreatic cancer in many epidemiological studies (3–8). Growing evidence from genome-wide association studies also has confirmed the association of *ABO* genetic polymorphisms (e.g., rs505922) with pancreatic cancer risk (9–11). In western populations, these studies have consistently shown that individuals with A, B, or AB blood group have a greater risk of pancreatic cancer than those with O blood group.

Histo-blood group antigens (HBGAs) are present in rich diversity in the mucosal epithelia of human respiratory, genitourinary, and digestive tracts, which serve as host immune receptor sites important for bacterial or viral attachment and infection (12). ABO antigens are also expressed on platelets. Their production and expression are encoded by gene families expressing ABO, secretor (*FUT2*), and Lewis-type (*FUT3*) antigens. The *ABO* gene produces either a functional glycosyltransferase that transfer specific sugar residues to a precursor substance (the H antigen) to make the A and B antigens, or a non-functional enzyme. ABO alleles (A, B, and O) in the *ABO* gene are tagged by single nucleotide polymorphisms (SNP) at the locus; rs505922 (as a proxy for rs8176719) marks the O allele and rs8176746 marks the B allele (4, 13). The activity of the ABO glycosyltransferase differs between two classes of A alleles, resulting in increased antigen presentation among carriers of the A^1 allele relative to carriers of the A^2 allele. This suggests that if the association between the A allele and a phenotype is mediated through antigen presentation, then the magnitude of the association with the A^1 allele should be greater than that for the

A^2 allele. Indeed, differential associations between the A^1 and A^2 alleles have been observed with venous thromboembolism (14) and PDAC (5).

Secretor status is determined by a SNP (rs601338) at the *FUT2* gene, which encodes an enzyme (galactoside 2-L-fucosyltransferase) that allows for the secretion of ABO antigens into gastrointestinal secretions and the expression of ABO antigens in mucosal epithelia (15). This suggests that secretor status may modify the association between ABO blood type and PDAC.

The *FUT3* gene on chromosome 19 is polymorphic and encodes an α (1,3/1,4)fucosyltransferase involved in the synthesis of Lewis antigens. These antigens are expressed in exocrine secretions and can be found on the surface of red blood cells (16). Previous studies found that some SNPs (e.g., rs812936, rs28362459, and rs3894326) at the *FUT3* locus were associated with a decrease in Lewis antigen enzyme activity (Lewis negative phenotype) (17–19). *FUT3* and *FUT2* interact to produce different forms of the Lewis antigen, resulting in the three common Lewis antigen phenotypes: Le(a-b-) (Lewis negative), Le(a+b-) (Lewis positive [Lewis a antigen] among non-secretors), and Le(a-b+) (Lewis positive [Lewis b antigen] among secretors).

Associations between secretor status and Lewis antigen activity have been investigated individually with ABO blood groups, but interactions between the three have not been reported. Particularly for pancreatic cancer, there has been only one study (our previous work) investigating secretor status and ABO blood group in relation to pancreatic cancer risk. That study, using PanScan consortium data, did not find a statistically significant difference between the odds ratio (OR) for non-O blood group versus O blood group among secretors and the OR among non-secretors (20), but it may have been underpowered to detect an interaction. Given current limited knowledge regarding the joint effects of secretor status, Lewis antigens and ABO blood groups on risk of PDAC, we combined data from the PanScan and PanC4 consortia to perform a population-based study including 8,027 pancreatic cancer cases and 11,362 controls with data on genetically derived ABO blood, secretor, and Lewis antigen groups. The current study more than doubles the sample size of our previous study, which only examined the interaction between ABO blood groups and *FUT2*.

Materials and Methods

Study participants

Our study included participants in the Pancreatic Cancer Cohort Consortium (PanScan I-III) and the Pancreatic Cancer Case-Control Consortium (PanC4) including 16 cohorts and 13 case-control studies genotyped in five previous genome-wide association studies (GWAS). Detailed information on cases and controls were previously described (9–11, 21–23). In brief, cases were defined as individuals with primary adenocarcinoma of the exocrine pancreas and those with non-exocrine pancreatic tumors were excluded. Each study in the consortia obtained informed consent from study participants and Institutional Review Board approvals. Of 23,064 participants, we excluded those with missing information on sex (n=1,502), those with missing genotype data (n=2,071), those with no genetically

derived blood, secretor, or Lewis groups (n=34), and those without covariates (n=68). After excluding these, data from 19,389 participants remained in our analysis (8,027 cases and 11,362 controls), all of European descent. Information on covariates was collected through written questionnaires or in-person interviews (4, 20). For this study, we obtained data on age and sex as covariates for analysis.

Genetically derived blood groups and antigens

We utilized SNP genotype data to define blood group alleles and genotypes for secretor status and Lewis antigens. Genotyping for participants in PanScan I-III was performed at the Cancer Genomics Research Laboratory of the National Cancer Institute using Illumina HumanHap series and Illumina Omni series arrays. For PanC4 participants, genotyping was performed at the Johns Hopkins Center for Inherited Disease Research using the Illumina HumanOmniExpressExome-8v1 array. Details about genotyping, quality control, and imputation procedure can be found elsewhere (11).

To determine *ABO* alleles (O, A, and B), we utilized haplotypes of two SNPs (rs505922 and rs8176746) that were highly correlated $(r^2 \approx 1)$ with the blood O and B alleles, respectively. We also used two additional SNPs, rs8176704 and rs574347, to define subtypes of the A allele (A^1 and A^2) (4, 20). For haplotype analysis, we used the 'haplo.stats' R package. To determine secretor status, we used the *FUT2* SNP rs601338 (G>A), and individuals with the homozygote A/A genotype were defined as non-secretors (20, 24). Genotypes of three other SNPs (rs812936, rs28362459, and rs3894326) on *FUT3* were used to determine Lewis antigen status (positive and negative). Previous studies found that these SNPs had good genotype-phenotype correlation in Caucasians and could identify Lewis negative individuals (16, 19). In this study, we determined ABO alleles (O, A, A^1, A^2, and B), secretor status, and Lewis antigen groups as shown in Supplementary Table 1. (Details of all 8 SNPs are presented in Supplementary Table 2.)

Statistical analysis

We compared the distributions of age, sex, blood group alleles, secretor status, and Lewis antigens in cases and controls. To assess the relationships of ABO blood group alleles, secretor status, and Lewis antigen groups with pancreatic cancer risk, we used unconditional logistic regression models and estimated ORs and 95% confidence intervals (CI) for pancreatic cancer risk adjusting for age and sex. To further explore relationships of ABO with secretor status and Lewis antigens, we additionally performed joint analysis of ABO blood group alleles (O vs. non-O allele; number of non-O alleles; O vs. A allele; number of A allele; number of A1 allele; number of A2 allele; O vs. B allele; number of B allele) with secretor status (secretor and non-secretor) and Lewis antigens (positive and negative), separately. In the joint analyses, multiplicative interactions were also evaluated between ABO groups and secretor status and between ABO groups and Lewis antigens adjusting for age and sex. For sensitivity analyses, we also examined the interactions with further adjustment for confounding factors, for example, diabetes, obesity, smoking, and alcohol drinking. In addition, we performed a three-way joint analysis of blood group (O vs. non-O), secretor (secretor or non-secretor), and Lewis antigens group (positive or negative) and tested the three-way interaction using likelihood ratio test. All statistical analyses were

conducted with the R software program (R version 3.6.3), and we reported two-sided p-values.

Data availability

The genotype and phenotype data used in this study are available through dbGAP (phs000206.v5.p3 for the PanScan and phs000648.v1.p1 for the PanC4). Covariate data we used are available via data sharing agreements upon request.

Results

The distributions of age, sex, blood group allele, secretor status and Lewis antigen groups in cases and controls is shown in Table 1. Study participants were largely in the range of age between 61 and 70 years (29% in cases and 38% in controls). The participants were a little more frequently men (54% of cases and 63% of controls), and the proportion of men was higher in controls than cases. The most common blood types were A among cases and O among controls, and the majority of both cases and controls were in the secretor group (78%) and had positive Lewis antigen (90%), i.e., normal or semi-normal function of the Lewis antigen.

We examined the associations of ABO blood alleles, secretor status, and Lewis antigen groups with the risk of pancreatic cancer (Table 2). As expected, non-O blood groups were associated with a greater risk of pancreatic cancer (adjusted OR [95% CI] = 1.39 [1.31–1.47]) compared to the O blood group. The risk was higher with increasing number of non-O alleles (adjusted OR [95% CI] = 1.36 [1.27–1.45] for one allele and 1.49 [1.36–1.63] for two alleles). Among the non-O blood groups, individuals who were homozygotes for the A blood group had the greatest risk of pancreatic cancer (adjusted OR [95% CI] = 1.76 [1.49–2.08] for the A^1A^2 subtype; adjusted OR [95% CI] per A allele = 1.22 [1.16–1.28] per A^1 allele, 1.13 [1.04–1.22] per A^2 allele). This is consistent with the hypothesis that individuals with the A^1 allele express more A antigen than individuals with the A^2 allele. When comparing risk estimates per allele between A and B, our study participants had a OR of 1.22 of pancreatic cancer risk per A allele (95% CI = 1.17–1.28) while they had a OR of 1.15 per B allele (95% CI = 1.07–1.24). Conversely, we observed no significant marginal associations of pancreatic cancer risk with secretor status and modest associations with Lewis antigen group (adjusted OR [95% CI] = 1.01 [0.95–1.09] and 1.10 [1.00–1.21], respectively).

We analyzed the joint association between ABO blood groups and secretor status in relation to pancreatic cancer risk (Table 3). We consistently observed greater risks of pancreatic cancer among individuals with non-O alleles among both secretors and non-secretors; however, the per-non-O-allele OR was greater among secretors than non-secretors (adjusted OR [95% CI] =1.30 [1.24–1.36] vs. 1.10 [1.00–1.20], respectively; p-interaction = 0.001). The difference in *ABO* allele ORs between secretors and non-secretors was greatest for the A^1 allele (adjusted OR [95% CI] per A^1 allele = 1.28 [1.21–1.35] vs. 1.01 [0.91–1.13]; p-interaction = 0.0002), while the differences in ORs were much smaller for A^2 and B alleles (adjusted OR [95% CI] = 1.13 [1.04–1.24] vs. 1.11 [0.93–1.32] for A^2 allele, 1.14 [1.05–1.24] vs. 1.18 [1.01–1.39] for B allele). In our sensitivity analysis, we assessed

the interaction effects of ABO blood groups and secretor status adjusting for additional pancreatic-related confounders such as diabetes, obesity, smoking, and alcohol drinking (Supplementary Table 3). All the effects of non-O alleles, in particular A^1, remained significant (all p-values ≤ 0.2). We also conducted joint associations for ABO blood groups and Lewis antigen (positive or negative) (Supplementary Table 4; Supplementary Table 5). We found no compelling evidence of effect-measure modification after adjusting for the confounders as the OR associated with non-O alleles were similar in Lewis positive and Lewis negative individuals.

We also performed a three-way joint analysis of non-O blood group with secretor status and Lewis antigen group (Figure 1; Supplementary Table 4). Individuals with non-O blood types had consistently higher risk relative to those with O blood type, regardless of secretor or Lewis status. Among individuals with O blood type who were also Lewis positive, secretors had lower risk than non-secretors (adjusted OR [95% CI] = 0.85 [0.76–0.96]; p=0.006), while those with O blood type who were Lewis negative, secretors and non-secretors had similar risks (adjusted OR [95% CI] = 0.94 [0.77–1.15] and 0.82 [0.58–1.14]; p=0.24 and 0.56, respectively). Additionally, we assessed the association between the risk of pancreatic cancer and different forms of the Lewis antigen predicted by combinations of *FUT2* and *FUT3* genotypes, regardless of their ABO blood group (Table 4). We found no difference in the risk among genetically inferred Lewis antigens marginal over *ABO* genotypes.

Discussion

This large population-based study confirms previous epidemiologic evidence that in western populations, non-O blood alleles are associated with greater risk of pancreatic cancer as compared with O blood alleles. In the subgroup analyses of A alleles (A^1 and A^2), we found that the A^1 allele was the larger contributor to the risk of pancreatic cancer associated with non-O alleles as compared to A^2 allele. Although we did not observe significant marginal associations of secretor status and pancreatic cancer, we found evidence of effect measure modification between *ABO* and *FUT2*: for example, the OR for non-O blood types relative to O blood types was 18% larger among secretors compared to non-secretors (p-interaction = 0.001). This multiplicative interaction appeared to be driven by the A^1 allele (p-interaction = 0.0002); the A^2 allele and B blood group did not have significant interaction effects with secretor status on pancreatic cancer risk.

The observed association between secretor status and risk of pancreatic cancer differed according to Lewis antigen status among individuals with O blood type: secretors had lower risk than non-secretors among Lewis positive individual, while secretors and non-secretors had similar risk among Lewis negative individuals. This is consistent with the biological interaction between Lewis antigens and secretor status: Lewis-positive secretors express a different Lewis antigen from non-secretors among Lewis positive individuals, while Lewis negative individuals do not express any Lewis antigen, regardless of secretor status. This association, if true, would indicate that Lewis antigens confer risk independent of blood group antigen expression. However, this observation should be interpreted with caution: the three-way statistical interaction between ABO blood type, secretor status and Lewis antigen

status was not significant in our analysis (p-interaction = 0.27), and there was no association between Lewis antigen status and pancreatic cancer risk marginal over ABO blood type.

Our findings on higher risk of pancreatic cancer in non-O blood groups are in line with previous studies on the ABO blood types and pancreatic cancer risk, including case-control studies from as early as the 1960s and 1970s (25–27). Two earlier studies including PanScan participants (one of which determined ABO blood types based on questionnaires and the other using genotype data) also found elevated risk of incident pancreatic cancer associated with A, B, or AB blood groups as compared to the O blood group (3, 4). Similarly, studies in other ethnic groups such as East Asians have identified a greater risk of pancreatic cancer among individuals with non-O blood types as compared to the risk among those with O blood type (e.g., OR = 1.6–1.7 for A vs. O blood type) (8, 28, 29).

In our study, among the non-O alleles, the A allele was associated with greater risk of pancreatic cancer than the B allele (e.g., adjusted per-allele OR [95% CI] = 1.22 [1.17–1.28] and 1.15 [1.07–1.24], respectively). This is consistent with a meta-analysis result of 24 studies (10,415 pancreatic cancer cases and 869,044 controls) that found a higher risk of pancreatic cancer associated with non-O blood groups (OR = 1.4, 1.2, and 1.3 for A, B, and AB, respectively) (8). However, it is still not clear which of the non-O blood groups (A, B, and AB) is associated with the highest risk of pancreatic cancer as compared to the O blood group, and there are conflicting results (4, 8, 30).

In addition, we found that the high risk associated with the A allele was mainly due to the A^1 allele, rather than the A^2 allele (e.g., adjusted per-allele OR [95% CI] = 1.22 [1.16–1.28] and 1.13 [1.04–1.22] for A^1 and A^2 allele, respectively), which is consistent with previous findings from our consortia data. For example, a matched case-control study of PanScan using the same four SNPs that we used to define ABO blood groups (20) observed that individuals with genotype A^1/O had an OR of 1.48 (95% CI = 1.23–1.78), and genotype A^1/A^1 had an OR of 1.71 (95% CI = 1.18–2.47) relative to those with genotype O/O, while those with A^2/O or A^1/A^2 had no significant associations. A previous large multicenter study within the PANcreatic Disease ReseArch (PANDoRA) consortium found that, as compared with the O allele, only A^1 carriers had an increased risk of pancreatic cancer [OR (95% CI) = 1.25 (1.02–1.51) for A^1/O, 1.57 (1.11–2.23) for A^1/A^1, and 1.71 (1.04–2.80) for A^1/A^2], while carriers of A^2 and B allele did not (5). However, more work is needed to solve the mechanism of how different glycosyltransferase activity is biologically related to the risk of pancreatic cancer.

Since *FUT2* gene encodes an enzyme (secretor) allowing the secretion of ABO antigens into body fluids (31, 32), we wanted to assess potential effects of the interplay between genetically derived ABO blood groups and secretor status on pancreatic cancer. Notably, we found significant interactions of secretor status with non-O alleles, particularly the A^1 allele, but not the A^2 allele and B allele. Our prior study of PanScan did not detect these interactions, despite being a matched case-control design, possibly due to the small study sample size (total n = 3,000) (20). However, the direction of the joint effects was consistent between our study and the previous study (i.e., a greater risk among individuals with non-O blood group and secretors). For other diseases and phenotypes, secretor status

has modified the disease associations with ABO blood groups. For example, a recent report observed that the non-secretor status reduced the risk of mortality among patients hospitalized with COVID-19; this reduction was larger among individuals with non-O blood groups, especially A blood group (33). Other studies reported that both *ABO* and *FUT2* were associated with serum lipase activity and pancreatitis risk(15), and that the association between non-O blood types and recurrent urinary tract infection was restricted to non-secretors(34). But in other studies, secretor status did not modify well-established associations between ABO blood group and disease (e.g., the inverse association between non-O blood types and venous thromboembolism(35)).

The joint effects of Lewis antigens, secretor, and ABO blood groups have long been studied for various diseases from infections (36–39) to common diseases including cancers (40–42). Lewis antigens may be particularly relevant for pancreatic cancer, as Lewis antigen status is associated with levels of carbohydrate antigen 19–9 (CA19-9), a biomarker for early detection of pancreatic cancer(43–47). In this study, we found that Lewis antigen status was not directly associated with pancreatic cancer risk and also did not have risk interactions with ABO blood groups. This suggests that Lewis status is associated with CA-19-9 levels in the presence of disease, but is not itself a risk factor or effect modifier. Our finding will require confirmation by other population-based studies in the future.

This study was based on two large consortia of pancreatic cancer data, the Pancreatic Cancer Cohort Consortium and the Pancreatic Cancer Case-Control Consortium, which provided a large number of pancreatic cancer cases from 16 cohorts and 13 case-control studies. Thus, the large sample size afforded sufficient statistical power enough to detect significant interaction effects across ABO, secretor, and Lewis antigens. Additionally, our results are unlikely to be confounded by population structure since all study participants were relatively genetically homogeneous (with a predominance of European ancestries).

Nevertheless, there are several limitations of our study to be noted. Although we adjusted for potential confounding effects of age and sex, there is a possibility of residual confounding effects from other risk factors of pancreatic cancer that were not adjusted for in our study. To complement it, we did sensitivity analyses to examine the effect modifications by secretor or Lewis activity adjusting for additional covariates such as diabetes, obesity, smoking, and alcohol drinking. Our findings remained the same despite some limitations on the covariates including missing data (up to 32%) and differences in data collection between case-control and cohort studies. Also, there is some chance of exposure misclassification because genetically determined exposure status might not be the same as the phenotype. For example, for Lewis antigens, a previous study reported significant divergence between genotypes and phenotypes (e.g., $p = 0.002$ for the difference in the frequencies of Lewis negative derived by genotypes and phenotypes [18% vs. 31%, respectively]) (48), and other studies have reported heterogeneity of Lewis antigen expression depending on host conditions such as H. pylori infection (49) or cancer progression (50). However, our main findings about *ABO* and secretor (*FUT2*) genotypes would be likely to have no misclassification bias as *ABO* genotypes and blood groups have showed high accuracy in a number of previous studies (51, 52), and *FUT2* genotype and secretor status also have been found to be highly correlated (20, 53). Lastly, including only European-ancestry individuals

limits the generalizability of our findings given that the *ABO*, secretor (*FUT2*), and Lewis antigen (*FUT3*) genotypes and their allele frequencies are different across ethnic groups. Hence, further genetic epidemiology studies including ethnically diverse populations are clearly warranted.

In conclusion, we found that the *FUT2* polymorphism determining secretor status modulates the associations between non-O blood alleles and the risk of pancreatic cancer. Particularly, secretor individuals with A blood alleles had a higher risk of pancreatic cancer than non-secretors with A alleles, and the effect modification by the secretor status was significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

PDAC	pancreatic adenocarcinoma (PDAC)
HBGAs	histo-blood group antigens
SNP	single nucleotide polymorphism
OR	odds ratio
GWAS	genome-wide association study
CI	confidence interval

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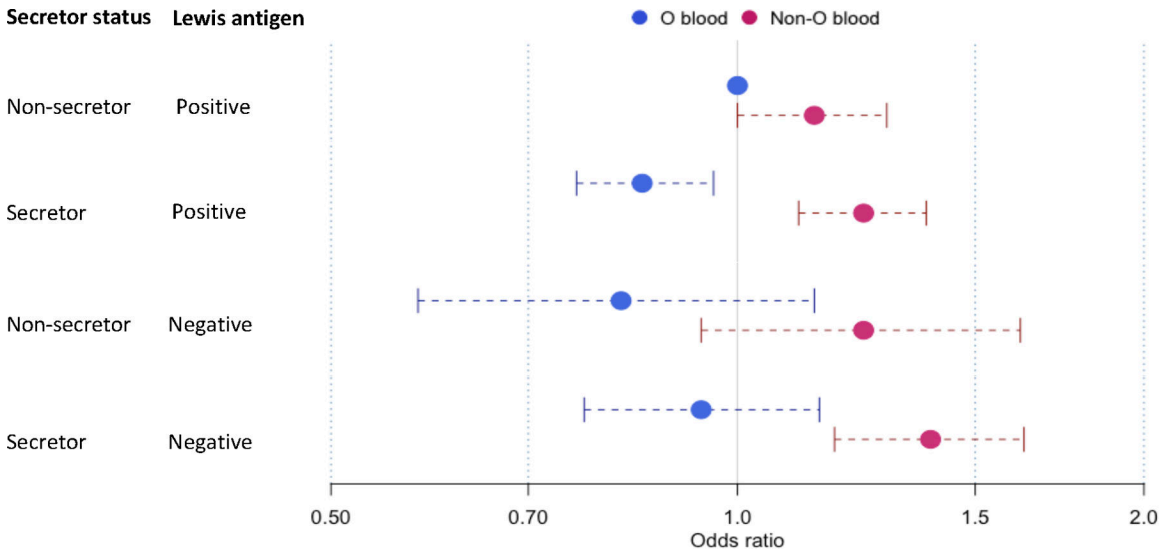

Figure 1. Joint analysis of secretor status (*FUT2*) and Lewis antigen (*FUT3*) in the relationship with pancreatic cancer, stratified by O and non-O blood group alleles.

The point estimates and 95% confidence intervals are presented as circles and error bars. The blue circle represents the O blood group and the red circle represents the non-O blood group. The reference group included non-secretors with positive Lewis antigen and O blood group allele.

Table 1.

Characteristics of study participants in PanScan I-III and PanC4

	Pooled data (n = 19,389)	
Variable	**Case (n = 8,027)**	**Control (n = 11,362)**
Age, n (%)		
< 51 years	1,377 (17.2)	1,545 (13.6)
51–60 years	2,074 (25.8)	2,464 (21.7)
61–70 years	2,323 (28.9)	4,329 (38.1)
71–80 years	1,704 (21.2)	2,580 (22.7)
> 80 years	549 (6.8)	444 (3.9)
Sex, n (%)		
Male	4,360 (54.3)	7,134 (62.8)
Female	3,667 (45.7)	4,228 (37.2)
ABO blood group, n (%)		
O	2,816 (35.1)	4,857 (42.7)
A	3,798 (47.3)	4,723 (41.6)
A^1O	2,398 (29.9)	2,902 (25.5)
A^2O	684 (8.5)	989 (8.7)
A^1A^1	375 (4.7)	486 (4.3)
A^1A^2 or A^2A^1	300 (3.7)	303 (2.7)
A^2A^2	41 (0.5)	43 (0.4)
B	999 (12.4)	1279 (11.3)
BO	916 (11.4)	1,192 (10.5)
BB	83 (1.0)	87 (0.8)
AB	414 (5.2)	503 (4.4)
A^1B	290 (3.6)	372 (3.3)
A^2B	124 (1.5)	131 (1.2)
Secretor status, n (%)		
Non-secretor	1,778 (22.2)	2,548 (22.4)
Secretor	6,249 (77.8)	8,814 (77.6)
Lewis antigen, n (%)		
Positive (normal or semi-normal)	7,189 (89.6)	10,259 (90.3)
Negative (no activity)	838 (10.4)	1,103 (9.7)

Table 2.

Associations of genotype-derived ABO blood group alleles, secretor status, and Lewis antigen with pancreatic cancer risk (n=19,389)

	Unadjusted Model	Adjusted[a] Model
	OR (95% CI)	**OR (95% CI)**
Blood group (ABO)		
(O vs. non-O type)		
O	1.00 (Ref)	1.00 (Ref)
Non-O	1.38 (1.30, 1.47)	1.39 (1.31, 1.47)
(Number of non-O alleles)		
0	1.00 (Ref)	1.00 (Ref)
1	1.36 (1.27, 1.44)	1.36 (1.27, 1.45)
2	1.47 (1.35, 1.61)	1.49 (1.36, 1.63)
Per non-O allele	1.25 (1.20, 1.30)	1.25 (1.20, 1.31)
(ABO blood groups)		
O	1.00 (Ref)	1.00 (Ref)
A	1.39 (1.30, 1.48)	1.39 (1.30, 1.48)
B	1.35 (1.23, 1.48)	1.35 (1.23, 1.49)
AB	1.42 (1.24, 1.63)	1.44 (1.25, 1.65)
(ABO blood subgroups)		
OO	1.00 (Ref)	1.00 (Ref)
A^1O	1.43 (1.33, 1.53)	1.42 (1.32, 1.53)
A^2O	1.19 (1.07, 1.33)	1.19 (1.07, 1.33)
A^1A^1	1.33 (1.15, 1.53)	1.34 (1.16, 1.55)
A^1A^2	1.71 (1.45, 2.02)	1.76 (1.49, 2.08)
A^2A^2	1.64 (1.07, 2.53)	1.64 (1.06, 2.53)
BO	1.33 (1.20, 1.46)	1.33 (1.21, 1.47)
BB	1.65 (1.21, 2.23)	1.63 (1.20, 2.22)
A^1B	1.34 (1.14, 1.58)	1.38 (1.18, 1.63)
A^2B	1.63 (1.27, 2.10)	1.58 (1.23, 2.03)
(Number of A alleles)		
0 (all other alleles)	1.00 (Ref)	1.00 (Ref)
1	1.28 (1.21, 1.36)	1.28 (1.20, 1.36)
2	1.38 (1.24, 1.54)	1.40 (1.26, 1.56)
Per A allele	1.22 (1.17, 1.28)	1.22 (1.17, 1.28)
Per A^1 allele	1.21 (1.16, 1.28)	1.22 (1.16, 1.28)
Per A^2 allele	1.13 (1.04, 1.22)	1.13 (1.04, 1.22)
(Number of B alleles)		
0 (all other alleles)	1.00 (Ref)	1.00 (Ref)

	Unadjusted Model	Adjusted[a] Model
	OR (95% CI)	**OR (95% CI)**
1	1.14 (1.05, 1.23)	1.15 (1.06, 1.24)
2	1.38 (1.02, 1.87)	1.37 (1.01, 1.86)
Per B allele	1.14 (1.07, 1.23)	1.15 (1.07, 1.24)
Secretor status (*FUT2*)		
Non-secretor	1.00 (Ref)	1.00 (Ref)
Secretor	1.02 (0.95, 1.09)	1.01 (0.95, 1.09)
Lewis antigen activity (*FUT3*)		
Positive (normal or semi-normal)	1.00 (Ref)	1.00 (Ref)
Negative (no activity)	1.08 (0.99, 1.19)	1.10 (1.00, 1.21)

[a]Adjusted for age and sex

Table 3.

Associations of ABO blood group alleles and pancreatic cancer by secretor status (*FUT2*) and interactions between ABO blood group alleles and secretor status

	Secretor (*FUT2*)		
	Non-secretor	Secretor	
	Adjusted[a] OR (95% CI)	Adjusted[a] OR (95% CI)	*P for interaction*
O v s. non-O			0.002
O blood group	1.00 (Ref)	0.88 (0.79, 0.98)	
Non-O blood group	1.17 (1.03, 1.32)	1.28 (1.15, 1.42)	
Number of non-O alleles			0.001
Per non-O allele	1.10 (1.00, 1.20)	1.30 (1.24, 1.36)	
Number of A alleles			0.0003
Per A allele	1.04 (0.95, 1.15)	1.28 (1.21, 1.35)	
Number of A^1alleles			0.0002
Per A^1 allele	1.01 (0.91, 1.13)	1.28 (1.21, 1.35)	
Number of A^2alleles			0.774
Per A^2 allele	1.11 (0.93, 1.32)	1.13 (1.04, 1.24)	
Number of B alleles			0.697
Per B allele	1.18 (1.01, 1.39)	1.14 (1.05, 1.24)	

[a]Adjusted for age and sex

Table 4.

Associations between different forms of Lewis antigen and the risk of pancreatic cancer

Lewis antigen (*FUT3 & FUT2*)	**Adjusted[a] OR (95% CI)**
Le(a−b+) (Lewis positive, secretor)	1.00 (Ref)
Le(a+b−) (Lewis positive, non-secretor)	1.00 (0.93, 1.08)
Le(a−b−) (Lewis negative)	1.00 (1.00, 1.21)

[a]Adjusted for age and sex