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Research Article

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Variant ABO Blood Group Alleles, Secretor Status, and Risk of Pancreatic Cancer: Results from the Pancreatic Cancer Cohort Consortium

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Abstract

Background: Subjects with non-O ABO blood group alleles have increased risk of pancreatic cancer. Glycosyltransferase activity is greater for the A_1 versus A_2 variant, whereas O01 and O02 variants are nonfunctioning. We hypothesized: 1) *A^1* allele would confer greater risk than *A^2* allele, 2) protective effect of the *O* allele would be equivalent for *O01* and *O02* variants, 3) secretor phenotype would modify the association with risk.

Methods: We determined ABO variants and secretor phenotype from single nucleotide polymorphisms in *ABO* and *FUT2* genes in 1,533 cases and 1,582 controls from 12 prospective cohort studies. Adjusted odds ratios (OR) for pancreatic cancer were calculated using logistic regression.

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Results: An increased risk was observed in participants with A^1 but not A^2 alleles. Compared with subjects with genotype *O*/*O*, genotypes A^2/O, A^2/A^1, A^1/O, and A^1/A^1 had ORs of 0.96 (95% CI, 0.72–1.26), 1.46 (95% CI, 0.98–2.17), 1.48 (95% CI, 1.23–1.78), and 1.71 (95% CI, 1.18–2.47). Risk was similar for *O01* and *O02* variant *O* alleles. Compared with *O01*/*O01*, the ORs for each additional allele of *O02*, A^1, and A^2 were 1.00 (95% CI, 0.87–1.14), 1.38 (95% CI, 1.20–1.58), and 0.96 (95% CI, 0.77–1.20); *P*-value, *O01* versus *O02* = 0.94, A^1 versus A^2 = 0.004. Secretor phenotype was not an effect modifier (*P*-interaction = 0.63).

Conclusions: Among participants in a large prospective cohort consortium, ABO allele subtypes corresponding to increased glycosyltransferase activity were associated with increased pancreatic cancer risk.

Impact: These data support the hypothesis that ABO glycosyltransferase activity influences pancreatic cancer risk rather than actions of other nearby genes on chromosome 9q34. *Cancer Epidemiol Biomarkers Prev; 19(12); 3140–9. ©2010 AACR.*

Introduction

The *ABO* gene encodes a glycosyltransferase with 3 main alleles (A, B, and O), with different substrate specificities (1). The A, B, and O glycosyltransferases transfer *N*-acetyl-D-galactosamine (GalNAc), D-galactose (Gal), and no sugar residue, respectively, to an oligosaccharide acceptor, known as the H histo-blood group antigen, which is expressed on the surface of red blood cells, endothelial cells, and epithelial cells, including the gastrointestinal mucosa (2).

Recent studies have shown an increased risk of pancreatic cancer in individuals with non-O blood type (A, AB, and B; refs. 3–5). In addition, a gene–dose effect has been noted, whereby each additional *A* or *B* allele is associated with a further increase in risk, compared with the *O* allele (6). In this study, we examined variants in the *ABO* and *FUT2* genes to further investigate a possible role for the ABO glycosyltransferase and ABO antigen expression in pancreatic cancer pathogenesis.

The A_1 glycosyltransferase is the predominant transferase underlying the A blood group. However, a variant transferase, known as A_2, is present in approximately 20% of White individuals. The A_2 phenotype is characterized by altered acceptor preference and a large reduction in transferase activity (7, 8). Therefore, the A^2 (or *A201*) allele results in an intermediate phenotype, with approximately 5-fold fewer and less complex A antigens on the cell surface, between the "full" enzymatic activity defined by the A^1 (or *A101*) allele and the nonfunctioning enzyme defined by the *O* allele. We hypothesized that the risk of pancreatic cancer in individuals with the A^2 allele would be intermediate between those with the A^1 allele and those with the *O* allele.

The *O* allele has 2 main variants, *O01* and *O02*, also known as O^1 and O^{1v}, respectively. These 2 variants share the same single nucleotide deletion at position 261 of the *ABO* gene, but they are dissimilar at numerous other positions, represent different phylogenetic lineages, and are thought to have arisen independently at distinct time points in evolution (9, 10). Therefore, the truncated proteins encoded by the *O01* and *O02* alleles are functionally the same (i.e., nonfunctional transferases) but exist on unique genetic backgrounds. We hypothesized that the risk of pancreatic cancer would be the same for individuals carrying *O01* and *O02* alleles, based on the assumption that the *ABO* gene product and not the genetic background, was the main factor leading to the association of *ABO* polymorphisms with pancreatic cancer risk.

The secretor phenotype is defined by the *FUT2* gene, a fucosyltransferase that catalyzes the addition of terminal α(1,2)fucose residues to produce the H antigen, an acceptor to which the ABO transferase adds its glycosyl groups (11). A functioning FUT2 enzyme allows for the secretion of ABO antigens into gastrointestinal secretions; however, homozygous inactivating mutations in *FUT2* occur in approximately 20% of individuals ("nonsecretors"; refs. 12, 13). We hypothesized that the association between ABO blood group alleles and pancreatic cancer risk was modified by secretor status, such that the association was stronger among secretors.

To investigate our 3 main hypotheses, we utilized genotype data from more than 3,000 subjects participating in 12 prospective cohort studies involved in the Pancreatic Cancer Cohort Consortium (PanScan) genome-wide association study (4, 6).

Materials and Methods

Study population

The PanScan genome-wide association study (GWAS) has been described previously, in detail (4, 6). It includes nested case–control studies from 12 prospective cohorts: Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC), CLUE II, American Cancer Society Cancer Prevention Study-II (CPS II); European Prospective Investigation into Cancer and Nutrition Study (EPIC); Health Professional's Follow-up Study (HPFS); New York University Women's Health Study (NYUWHS); Nurses' Health Study (NHS); Physicians' Health Study I (PHS I); Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO); Shanghai Men's and Women's Health Study (SMWHS); Women's Health Initiative (WHI); and Women's Health Study (WHS). In each cohort, a defined population of subjects was followed prospectively with assessments of lifestyle factors and

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ascertainment of cancer diagnoses. Cases included subjects with incident primary pancreatic adenocarcinoma (ICD-O-3 code C250-C259 or C25.0-C25.3, C25.7-C25.9). All subjects with nonexocrine pancreatic tumors (C25.4, histology type, 8150, 8151, 8153, 8155, 8240, and 8246) were excluded. Each cohort study selected participants with blood or buccal cells collected prior to cancer diagnosis. Incident pancreatic cancer cases identified by self-report, report of next-of-kin or through national death indices were typically confirmed by subsequent medical record review, linkage with a cancer registry, or both, without prior knowledge of genetic data.

One control was selected per case within each cohort. Controls were matched on year of birth (±5 years), gender, self-reported race/ethnicity, and source of DNA (peripheral blood or buccal cells). Controls were alive without pancreatic cancer on the incidence date of the matched case. Four cohorts (HPFS, NHS, PHS, and WHS) were additionally matched on smoking status (never, former, and current), and some cohorts were also matched on age at baseline (±5 years), age at blood draw (±5 years), date/time of day of blood draw, or fasting status at blood draw. Each cohort obtained informed consent from study participants and approval from its Institutional Review Board. The Special Studies Institutional Review Board of the National Cancer Institute approved the pooled PanScan study.

Assessment of ABO blood group alleles

Detailed methods and quality control procedures for genotyping by PanScan can be found elsewhere (4). We utilized single nucleotide polymorphism (SNP) data collected in the PanScan GWAS using the Illumina 550 HumanHap assay to define blood group subtype alleles and secretor phenotype. If the causative SNP was not available as part of the GWAS, we used SNPs in high linkage disequilibrium with the causative SNP to mark the appropriate phenotype. As described previously, rs505922 marked the *O* allele and rs8176746 marked the *B* allele (6, 14). Additionally, we used rs8176704 to mark the A^2 allele and rs574347 to mark the *O02* allele. The SNP rs601338 (G > A) defines secretor status in Whites (11), and individuals with the homozygote A/A genotype are nonsecretors. Because rs601338 is not genotyped by the Illumina 550 HumanHap array, we used the AC haplotype of rs602662 and rs281377 to infer secretor status; this haplotype is in perfect linkage disequilibrium ($r^2 = 1$) with the rs601338 A allele. Of note, secretor status is recessive, such that 2 nonsecretor alleles are necessary to manifest the nonsecretor phenotype. Using haplotypes of the above SNPs for each participant, we determined ABO alleles (*O01*, *O02*, A^1, A^2, and *B*) and secretor status (secretor, nonsecretor), as shown in Table 1. All haplotypes could be inferred with

Table 1. ABO blood group subtype alleles (A) and secretor status (B) among pancreatic cancer cases and nested controls in 12 prospective cohort studies[a]

(A)	Cases *n* (%)	Controls *n* (%)	rs505922	rs8176746	rs8176704	rs574347
No. of participants	1,533	1,582				
A blood group alleles	943 (31)	847 (27)				
A^1 alleles	729 (77)	611 (72)	C	C	G	T
A^2 alleles	214 (23)	236 (28)	C	C	A	T
O blood group alleles[b]	1,773 (58)	2,018 (64)				
O01 alleles	1,108 (63)	1,268 (63)	T	C	G	T
O02 alleles	643 (37)	733 (37)	T	C	G	C
B blood group alleles	350 (11)	299 (9)	C	A	G	T
(B)	**Cases *n* (%)**	**Controls *n* (%)**	**rs601338**			
Secretor status[c]						
Secretor	1,103 (81)	1,145 (79)	G/G or G/A			
Nonsecretor	261 (19)	297 (21)	A/A			

[a]Single nucleotide polymorphism (SNP) data collected in the PanScan genome-wide association study were used to define blood group subtype alleles and secretor phenotype. As shown, the single nucleotide changes at rs505922, rs8176746, rs8176704, rs574347, and rs601338 were used to mark the relevant alleles.

[b]The number of *O01* and *O02* alleles do not sum to the number of *O* alleles, as blood group O subtype could not be accurately imputed for 39 *O* alleles.

[c]Secretor status is recessive, such that 2 nonsecretor alleles are necessary to manifest the nonsecretor phenotype. Secretor status was successfully imputed for 2,806 of the 2,840 White subjects.

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greater than 99% posterior probability for each subject, using an EM algorithm to impute missing phase (14).

Assessment of covariates

Across all 12 participating cohorts, covariates were collected though written questionnaires or inperson interviews. Detailed descriptions of data collection methods have been published previously (6). We obtained data from each cohort on participants' age, gender, race/ethnicity (White, Asian, African, other), body mass index (BMI), smoking status (current, past, never), and history of diabetes (yes, no).

Statistical analyses

ABO blood group subtype alleles and secretor status were examined for cases and controls, and the distribution of blood type alleles in our study was compared with that seen in other comparable populations. We used unconditional logistic regression to calculate odds ratios (OR) and 95% CIs for pancreatic cancer by ABO blood group subtype alleles, adjusted for age, gender, race/ethnicity, cohort, smoking status, BMI, and history of diabetes. We repeated our analyses limited to White subjects. In addition, our previous studies (4, 6) showed little change in our results after adjusting for 5 principal components of population substructure determined using the entire set of the nearly 550,000 SNPs with the EIGENSTRAT program (4, 15). We assessed effect-measure modification by secretor phenotype (secretor vs. nonsecretor); the test for modification was assessed by entering the cross-product of blood group (non-O vs. O blood group) and secretor status into the model. We showed previously the lack of heterogeneity across the 12 cohorts for the association between blood group and pancreatic cancer risk using Cochran's Q-statistic [$P = 0.91$ for the comparison of non-O blood group (i.e., A, AB, or B) to O blood group across cohorts; refs. 6, 16]. All statistical analyses were done using the SAS 9.1 statistical package (SAS Institute), and all P-values were 2-sided.

Results

From the 12 participating cohorts, 1,533 pancreatic cancer cases and 1,582 controls were available for analysis. Clinical characteristics of the cases and controls were described previously (6). The frequency distributions of ABO subtype alleles and secretor status were highly similar among our control participants and subjects in previous studies (11, 17–20). Among controls, 72% of A alleles were A^1 and 28% were A^2, 63% of O alleles were $O1$ and 37% were $O2$, and 79% were secretors and 21% were nonsecretors (Table 1).

To address the hypothesis that inheritance of an A^1 allele would confer a greater risk of pancreatic cancer than an A^2 allele, we estimated ORs for combinations of O, A^1, and A^2 alleles, compared with O/O as the referent (Table 2). Compared with subjects with genotype O/O, those with genotype A^2/O had OR of 0.96 (95% CI, 0.72–1.26), genotype A^2/A^1 had OR 1.46 (95% CI, 0.98–2.17), genotype A^1/O had OR 1.48 (95% CI, 1.23–1.78), and genotype A^1/A^1 had OR 1.71 (95% CI, 1.18–2.47). Only 12 cases and 8 controls inherited an A^2/A^2 genotype, limiting our ability to accurately assess risk for subjects with this genotype. These data suggested that risk

Table 2. Age-adjusted and multivariable-adjusted ORs (95% CIs) for incident pancreatic cancer by blood group A subtype alleles

Second allele		First allele		
		O	A^1	A^2
O	No. of cases/controls	511/657	441/381	113/145
	Age-adjusted OR	1.0	1.48 (1.24–1.77)	1.00 (0.76–1.31)
	Multivariable-adjusted OR[a]	1.0	1.48 (1.23–1.78)	0.96 (0.72–1.26)
	Multivariable-adjusted OR[b]	1.0	1.47 (1.22–1.78)	0.94 (0.71–1.25)
A^1	No. of cases/controls	-	74/57	60/51
	Age-adjusted OR		1.68 (1.17–2.42)	1.48 (1.00–2.19)
	Multivariable-adjusted OR[a]		1.71 (1.18–2.47)	1.46 (0.98–2.17)
	Multivariable-adjusted OR[b]		1.89 (1.27–2.81)	1.46 (0.97–2.18)
A^2	No. of cases/controls	-	-	12/8
	Age-adjusted OR			1.92 (0.78–4.74)
	Multivariable-adjusted OR[a]			1.89 (0.76–4.73)
	Multivariable-adjusted OR[b]			1.90 (0.76–4.76)

[a] Multivariable adjustment by age, gender, race/ethnicity, cohort, smoking status, body mass index, and history of diabetes mellitus, in the entire study population.

[b] Multivariable adjustment by age, gender, cohort, smoking status, body mass index, and history of diabetes mellitus, in White participants only.

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Table 3. Age-adjusted and multivariable-adjusted ORs (95% CIs) for incident pancreatic cancer by number of blood group subtype alleles

Allele		OR for each additional allele (0, 1, 2)	*P*-value (*O01* vs. *O02*)	*P*-value (A^1 vs. A^2)
O01	Age-adjusted OR	1.0	0.84	–
	Multivariable-adjusted OR[a]	1.0	0.94	
	Multivariable-adjusted OR[b]	1.0	0.72	
O02	Age-adjusted OR	1.01 (0.89–1.16)	–	–
	Multivariable-adjusted OR[a]	1.00 (0.87–1.14)		
	Multivariable-adjusted OR[b]	1.03 (0.89–1.18)		
A^1	Age-adjusted OR	1.37 (1.20–1.58)	–	0.009
	Multivariable-adjusted OR[a]	1.38 (1.20–1.58)		0.004
	Multivariable-adjusted OR[b]	1.42 (1.23–1.64)		0.003
A^2	Age-adjusted OR	1.00 (0.80–1.24)	–	–
	Multivariable-adjusted OR[a]	0.96 (0.77–1.20)		
	Multivariable-adjusted OR[b]	0.96 (0.77–1.20)		

[a]Multivariable adjustment by age, gender, race/ethnicity, cohort, smoking status, body-mass index, and history of diabetes mellitus, in the entire study population.

[b]Multivariable adjustment by age, gender, cohort, smoking status, body-mass index, and history of diabetes mellitus, in White participants only.

associated with inheritance of an A^2 allele was less than that of inheriting an A^1 allele and similar to that of inheriting an O allele. We evaluated this further by classifying cases and controls by the number of inherited A^1 and A^2 alleles (0, 1, or 2; Table 3). For inheritance of each additional A^1 allele, the OR for pancreatic cancer was 1.38 (95% CI, 1.20–1.58). In contrast, for inheritance of each additional A^2 allele, the OR for pancreatic cancer was 0.96 (0.77–1.20; *P*-value for comparison = 0.004), again suggesting that the risk for pancreatic cancer with inheritance of an A^2 allele was less than that with inheritance of an A^1 allele.

To address the hypothesis that inheritance of an *O01* allele would confer a similar protective effect to inheriting an *O02* allele, we estimated ORs for combinations of *O01* and *O02* alleles, compared with non-O blood groups (A, AB, and B) as the referent (Table 4). For each combination of *O* allele subtypes, that is *O01*/*O01*, *O01*/*O02*, and *O02*/*O02*, ORs were highly similar to each other and to the OR for the *O*/*O* genotype. We evaluated this further by classifying cases and controls by the number of inherited *O01* and *O02* alleles (0, 1, or 2; Table 3). With *O01*/*O01* as the referent, the inheritance of each additional *O02* allele resulted in an OR for pancreatic cancer of 1.00 (95% CI, 0.87–1.14; *P*-value for comparison = 0.94), indicating a similar protective effect for inheritance of either *O01* or *O02* alleles.

To address the hypothesis that secretor status is an effect modifier of ABO blood type and pancreatic cancer risk, we estimated ORs for participants with secretor/O blood type, nonsecretor/non-O blood type, and secretor/non-O blood type, compared with nonsecretor/O blood type as the referent in Whites (Table 5). An increased risk of pancreatic cancer was observed in participants with non-O blood type, irrespective of secretor status (OR, 1.33; 95% CI, 0.94–1.87, among nonsecretors; OR, 1.51; 95% CI, 1.13–2.01, among secretors; *P*-interaction = 0.63).

Discussion

We investigated 3 hypotheses related to ABO glycosyltransferase activity and pancreatic cancer risk among more than 3,000 cases and controls from 12 large prospective cohort studies. First, the association of cancer risk with the *A* allele seems predominantly due to the A_1 glycosyltransferase, which has greater enzymatic activity than the A_2 glycosyltransferase. In our analysis, the less active A_2 glycosyltransferase did not increase risk of pancreatic cancer in comparison with the nonfunctioning O glycosyltransferase, despite giving rise to blood group A. Second, the protective effect of the *O* allele was essentially identical for the 2 main *O* allele variants, which share the same point mutation that abolishes enzyme activity but otherwise exist on distinct genetic backgrounds. Third, the association of pancreatic cancer risk with blood group was not statistically significantly modified by secretor status.

Older studies examining serologically determined ABO blood group and pancreatic cancer risk were inconsistent (21–25). Recently, epidemiologic studies and the PanScan GWAS showed an increased risk of pancreatic cancer in subjects with non-O blood group (A, AB, and B) compared with those with blood group O (3–5). Of note, the most statistically significant SNPs identified in the PanScan GWAS were located in the first intron of the *ABO* gene, in high linkage disequilibrium with the single base deletion that defines blood group O (4). A follow-up

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Table 4. Age-adjusted and multivariable-adjusted ORs (95% CIs) for incident pancreatic cancer by blood group O subtype alleles

O alleles		Non-O blood group (A, AB, and B)	O blood group
O/O	No. of cases/controls	1,016/918	497/648
	Age-adjusted OR	1.0	0.69 (0.60–0.80)
	Multivariable-adjusted OR[a]	1.0	0.69 (0.60–0.81)
	Multivariable-adjusted OR[b]	1.0	0.70 (0.60–0.82)
O01/O01	No. of cases/controls	1,016/918	192/250
	Age-adjusted OR	1.0	0.70 (0.56–0.86)
	Multivariable-adjusted OR[a]	1.0	0.71 (0.57–0.88)
	Multivariable-adjusted OR[b]	1.0	0.72 (0.58–0.90)
O01/O02	No. of cases/controls	1,016/918	240/303
	Age-adjusted OR	1.0	0.71 (0.59–0.87)
	Multivariable-adjusted OR[a]	1.0	0.71 (0.58–0.86)
	Multivariable-adjusted OR[b]	1.0	0.76 (0.62–0.93)
O02/O02	No. of cases / controls	1,016/918	65/95
	Age-adjusted OR	1.0	0.62 (0.45–0.86)
	Multivariable-adjusted OR[a]	1.0	0.60 (0.43–0.84)
	Multivariable-adjusted OR[b]	1.0	0.65 (0.46–0.93)

[a]Multivariable adjustment by age, gender, race/ethnicity, cohort, smoking status, body-mass index, and history of diabetes mellitus, in the entire study population.

[b]Multivariable adjustment by age, gender, cohort, smoking status, body-mass index, and history of diabetes mellitus, in White participants only.

study noted a remarkably consistent increase in risk for non-*O*/*O* genotypes across 12 separate prospective cohorts and a gene–dose effect, whereby each additional non-*O* allele further increased a subject's risk for pancreatic cancer (6).

The nucleotide sequence of the *ABO* gene was elucidated in 1990 (26, 27), and numerous allelic variants have been identified since that time (8). The human ancestral *ABO* gene is thought to have encoded the A_1 glycosyltransferase, with accumulation of subsequent nucleotide alterations in this consensus sequence leading to generation of the A^2, *B*, *O01*, and *O02* alleles (10, 28). The A^2 allele is characterized by a single base deletion in a stretch of 3 consecutive cytosine residues at nucleotides 1,059 to 1,061. This deletion shifts the open reading frame of *ABO*, resulting in 21 extra amino acids in the C-terminal domain and a protein with 30- to 50-fold lower transferase activity than the parent A_1 glycosyltransferase (7).

Actual biological consequences have been suggested previously in humans for the reduced enzymatic activity of the A_2 glycosyltransferase, most clearly in relation to circulating levels of von Willebrand factor (vWF) and the risk of venous thromboembolism (VTE). The ABO

Table 5. Age-adjusted and multivariable-adjusted ORs (95% CIs) for incident pancreatic cancer by ABO blood group and secretor status in Whites

Secretor status	O blood group	Non-O blood group	*P*-interaction
Nonsecretor			
No. of cases/controls	100/134	161/163	
Age-adjusted OR	1.0	1.33 (0.95–1.86)	0.63
Multivariable-adjusted OR[a]	1.0	1.33 (0.94–1.87)	0.63
Secretor			
No. of cases/controls	354/468	749/677	
Age-adjusted OR	1.02 (0.76–1.36)	1.48 (1.12–1.96)	
Multivariable-adjusted OR[a]	1.03 (0.77–1.39)	1.51 (1.13–2.01)	

[a]Multivariable adjustment by age, gender, cohort, smoking status, body mass index, and history of diabetes mellitus.

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glycosyltransferase attaches sugar residues to vWF, which is subsequently secreted into the circulation. In subjects with blood group O, vWF is cleared more quickly (29, 30), resulting in approximately 25% lower levels of circulating vWF than in subjects with blood groups A or B (31) and a lower risk of VTE (32, 33). The A_2 glycosyltransferase loads a lesser amount of A antigen onto vWF, compared with the A_1 transferase (34), and the A^2 allele is associated with lower circulating vWF levels than the A^1 or *B* alleles. Furthermore, the risk of VTE with the A^2 allele is comparable with that with the *O* allele, and reduced in comparison with the A^1 and *B* alleles, which code for more active transferases (32, 33). Therefore, the differing glycosyltransferase activity resulting from the A^1 and A^2 alleles is biologically relevant to a disease outcome (i.e., VTE) and seems to be directly related to the efficiency of glcosyl group transfer to a target molecule (i.e., vWF). Similarly, we noted a statistically significant increase in the risk of pancreatic cancer in subjects with the A^1 allele but not with the A^2 allele, which we believe further implicates ABO glycosyltransferase activity in the pathogenesis of pancreatic cancer.

The *O* allele is characterized by a single base deletion in the *ABO* gene at nucleotide 261. This deletion shifts the open reading frame of *ABO*, resulting in a premature stop codon and a truncated, nonfunctional protein (35). The *O* allele has 2 main variants, *O01* and *O02*, which share the 261 deletion. However, they are dissimilar at numerous other positions in exonic, intronic, and upstream and downstream regulatory regions (35–37). In fact, phylogenetic studies have suggested that the *O01* and *O02* alleles have distinct genetic backgrounds and acquired the 261 deletion as separate mutational events (10, 38). In this study, the protective effect of the *O* allele on pancreatic cancer risk was nearly identical for the *O01* and *O02* alleles, further supporting ABO glycosyltransferase activity, as opposed to genetic background, as the predisposing factor for pancreatic cancer risk.

The secretor phenotype is defined by the *FUT2* gene, a fucosyltransferase that catalyzes the addition of terminal α(1,2)fucose residues to produce the H antigen, the primary precursor to which the ABO enzyme adds its glycosyl groups. Across diverse populations, approximately 20% of individuals have homozygous loss of function mutations in *FUT2* due to creation of premature stop codons (11). These individuals have no ABO antigens in their gastrointestinal secretions, and such "nonsecretors" have reduced susceptibility to multiple pathogens, including noroviruses (39), *Helicobacter pylori* (40), and *Campylobacter jejuni* (41), due to decreased pathogen adherence to the mucous layer and epithelial cells lining the gastrointestinal tract (42). Furthermore, serum levels of vitamin B_{12} have been associated with secretor status, possibly as a consequence of susceptibility to chronic infection by *H. pylori* (43, 44). We hypothesized that secretor status might also modify the association of non-O blood groups with an increased risk of pancreatic cancer. Although a slightly higher risk was noted among secretors, this did not approach statistical significance. Interestingly, data are inconsistent for effect modification of the association between non-O blood groups and risk of VTE by secretor status, and this remains an area of continued investigation (45, 46).

These data suggest that ABO glycosyltransferase activity may play an important role in pancreatic tumorigenesis. Nevertheless, the underlying mechanisms linking the ABO glycosyltransferase with pancreatic cancer risk are not currently clear. One obvious hypothesis would be that the enzymatic activity of the ABO transferase impacts the processing and clearance of molecules that promote tumorigenesis. This would be analogous to the role of the ABO glycosyltransferase in determining levels of circulating vWF and risk of VTE. Interestingly, in 5 recent studies, SNPs at the *ABO* gene locus were found to be genetic determinants of circulating levels of soluble E-selectin, soluble P-selectin, soluble intercellular adhesion molecule-1 (ICAM-1), and tumor necrosis factor-alpha (TNF-α; refs. 18, 47–50. In each of these studies, the most statistically significant SNPs were proxies for defining the *O* versus non-*O* allele. These molecules are important mediators of chronic inflammation and immune cell recruitment and suggest interesting pathways for interrogation, particularly in light of the importance of stroma and tumor–host interactions in pancreatic cancer development (51).

Our study has several possible limitations. Using genetic data from a previously completed GWAS, we determined *ABO* alleles and secretor status using SNPs in high linkage disequilibrium with the causative nucleotide changes. Therefore, some degree of exposure misclassification remains a possibility. However, we have shown previously that *ABO* genotypes determined in this manner are highly accurate (6). In addition, the genetic map of the *ABO* locus has been investigated for more than 20 years, and numerous previous studies have genetically determined *ABO* alleles with high accuracy using a variety of methodologies (17, 19, 20). Moreover, any resultant misclassification due to measurement error is likely to be nondifferential in nature and therefore attenuate, rather than exaggerate, our findings.

Our study population was composed primarily of White participants, which somewhat limits the generalizability of our results. However, other risk factors for pancreatic cancer do not seem to differ substantially by race/ethnicity and the associations did not differ materially between the White and non-White subjects in this study. Nonetheless, further investigations that include more diverse study populations are warranted. Our power was somewhat limited to detect a statistically significant difference in the association between ABO blood group and pancreatic cancer risk among secretors compared with nonsecretors, given that only 20% of subjects were nonsecretors. Further analyses may be warranted of secretor status and pancreatic cancer risk in larger patient populations.

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Our study has several notable strengths. The PanScan provided a large number of pancreatic cancer cases from 12 cohort studies, and the prospective design of these cohorts minimized the potential for survival or selection biases. The risk of detecting a false association due to population stratification was relatively low, given the inclusion of prospective cohorts with homogeneous ethnic compositions, the primarily non-Hispanic European ancestry of the full study population, and the paucity of evidence for variation in pancreatic cancer risk in the ancestral population (52, 53). In addition, we showed previously that our results did not change after adjusting for potential population stratification bias by including the top 5 principal components of genetic variation as covariates in our logistic regression models (4, 6).

There remains only a limited understanding of the genetic determinants and initiating molecular events for pancreatic cancer. Our results suggest that the ABO glycosyltransferases may play an important role in pancreatic tumorigenesis. Further work is necessary to better understand the mechanisms that may underlie the association of ABO glycosyltransferase activity and resultant ABO carbohydrate phenotype with pancreatic cancer risk. The use of model systems of pancreatic cancer to further this work deserves particular consideration.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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