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Cancer Research

Pancreatic Cancer Risk and ABO Blood Group Alleles: Results from the Pancreatic Cancer Cohort Consortium

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Abstract

A recent genome-wide association study (PanScan) identified significant associations at the ABO gene locus with risk of pancreatic cancer, but the influence of specific ABO genotypes remains unknown. We determined ABO genotypes (OO, AO, AA, AB, BO, and BB) in 1,534 cases and 1,583 controls from 12 prospective cohorts in PanScan, grouping participants by genotype-derived serologic blood type (O, A, AB, and B). Adjusted odds ratios (ORs) for pancreatic cancer by ABO alleles were calculated using logistic regression. Compared with blood type O, the ORs for pancreatic cancer in subjects with types A, AB, and B were 1.38 [95% confidence interval (95% CI), 1.18–1.62], 1.47 (95% CI, 1.07–2.02), and 1.53 (95% CI, 1.21–1.92), respectively. The incidence rates for blood types O, A, AB, and B were 28.9, 39.9, 41.8, and 44.5 cases per 100,000 subjects per year. An increase in risk was noted with the addition of each non-O allele. Compared with OO genotype, subjects with AO and AA genotype had ORs of 1.33 (95% CI, 1.13–1.58) and 1.61 (95% CI, 1.22–2.18), whereas subjects with BO and BB genotypes had ORs of 1.45 (95% CI, 1.14–1.85) and 2.42 (1.28–4.57). The population attributable fraction for non-O blood type was 19.5%. In a joint model with smoking, current smokers with non-O blood type had an adjusted OR of 2.68 (95% CI, 2.03–3.54) compared with nonsmokers of blood type O. We concluded that ABO genotypes were significantly associated with pancreatic cancer risk. *Cancer Res; 70(3); 1015–23. ©2010 AACR.*

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Table 1. Characteristics by genotype-derived ABO blood type among control participants

Characteristic	Genotype-derived ABO blood type			
	O	A	AB	B
No. of control participants	657	642	89	195
Mean age (y, ± SD)	69.6 ± 7.5	68.9 ± 8.4	70.3 ± 5.9	69.3 ± 7.6
Female gender (%)	54.0	50.2	48.3	50.8
White race/ethnicity (%)	92.9	94.1	86.5	84.1
Smoking status (%)				
Current	19.8	25.2	21.4	26.7
Past	37.9	31.2	44.9	28.7
Never	41.3	42.1	31.5	42.6
Unknown	1.1	1.6	2.3	2.1
Mean BMI (kg/m^2) ± SD	26.5 ± 4.5	26.4 ± 4.6	25.2 ± 4.2	26.1 ± 4.4
History of diabetes mellitus (%)	6.2	7.3	5.6	5.1

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related mortality in Western societies, and >95% of patients who develop pancreatic cancer will die from the disease (1). Several highly penetrant but rare genetic alterations that have been identified predispose individuals to pancreatic cancer, but predisposing genetic alterations remain unknown for the vast majority of patients who develop this disease (2).

Work by Dr. Karl Landsteiner in the early 20th century led to the identification of three blood groups, forming the basis of transfusion medicine (3). A single gene on chromosome 9q34 was ultimately found to define a person's blood group, and its nucleotide sequence was elucidated in 1990 (4, 5). The *ABO* gene encodes a glycosyltransferase with three main variant alleles (A, B, and O), with different substrate specificities (6). The A, B, and O glycosyltransferases transfer *N*-acetylgalactosamine, D-galactose, and no sugar residue, respectively, to a protein backbone, known as the H antigen, which is expressed on the surface of RBC and numerous other tissues throughout the body (7). A role for ABO blood group antigens in human diseases has been suspected for several decades (8, 9), although an association with pancreatic cancer risk has been inconsistent (9–14).

A recent genome-wide association study (GWAS) among pancreatic cancer cases and controls (PanScan) found that several single nucleotide polymorphisms (SNP) at the *ABO* gene locus were among the most statistically significant associations with pancreatic cancer risk (15). However, the nature of this association and the influence of specific ABO genotypes on the risk of pancreatic cancer remain unknown. We hypothesized that defining a subject's ABO blood group alleles might provide additional risk information and provide supportive evidence for the role of ABO glycosyltransferase specificity in pancreatic tumorigenesis. Therefore, we used the genotype data from more than 3,000 subjects in 12 prospective cohort studies participating in PanScan to impute individual ABO alleles and determine their association with pancreatic cancer risk. This allowed us to investigate the full range of genotypic variation at the *ABO* gene locus (OO, AO, AA, AB, BO, and BB), as well as the ABO serotype (O, A, B, and AB) inferred from ABO genotypes. In addition, our nested prospective design allowed for rigorous investigation of interactions between known risk factors for pancreatic cancer and ABO blood group alleles.

Materials and Methods

Study population. The Pancreatic Cancer Cohort Consortium 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

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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Average age-adjusted population rates weighted by gender for U.S. whites 50 years and older were obtained from the Surveillance, Epidemiology, and End Results data (http://seer.cancer.gov/statistics/, accessed January 22, 2009).

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Table 2. Distributions of ABO alleles among control participants and comparable reference populations

SNPs			ABO allele distributions		
ABO alleles	rs505922	rs8176746	All controls* (%)	White controls (%)†	Reference populations‡ (%)
O	T	C	63.8	64.3	61–66
A	C	C	26.8	27.0	24–29
B	C	A	9.5	8.7	6–11

*All controls from PanScan, regardless of race/ethnicity (n = 1,583).
†Only White controls from PanScan (n = 1,455).
‡White populations from the published literature: refs. 14, 16, and 22–25.

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); 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). See Supplementary Table S1 for the list of participating cohorts with corresponding methodologic references. In each cohort, a defined population of subjects was followed prospectively with repeated assessments of lifestyle factors and 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 before cancer diagnosis. Incident pancreatic cancer cases identified by self-report, report of next of kin, or through national death indices were 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 (NCI) approved the pooled PanScan study.

Assessment of ABO blood group alleles. Detailed methods for genotyping by PanScan can be found elsewhere (15). Haplotypes of rs687289 and rs8176746 are perfectly correlated (r^2 = 1) with the O and B alleles, respectively, in the 60 HapMap phase 2 Centre d'Etude du Polymorphisme Humain European founders (16). Because rs687289 was not genotyped as part of PanScan, we used rs505922, which is a perfect surrogate for rs687289 in all HapMap phase 2 samples. Using rs505922 and rs8176746, all subjects' phased haplotype pairs could be inferred using an expectation-maximization algorithm with >99% posterior probability (17). Because each subject has two ABO alleles, six genotypes were possible: OO, AO, AA, AB, BO, and BB.

In the HPFS and NHS, participants self-reported ABO status as defined serologically (O, A, AB, or B) in 1996. In a validation study of these two cohorts, self-reported ABO

Table 3. Age-adjusted and multivariable-adjusted ORs (95% CIs) for incident pancreatic cancer by genotype-derived ABO blood type

	O	A	AB	B
No. of cases/controls	511/657	700/642	97/89	226/195
Age-adjusted OR	1.0	1.39 (1.19–1.63)	1.43 (1.05–1.95)	1.51 (1.21–1.89)
Multivariable-adjusted OR*	1.0	1.38 (1.18–1.62)	1.47 (1.07–2.02)	1.53 (1.21–1.92)
Multivariable–adjusted OR†	1.0	1.38 (1.17–1.63)	1.45 (1.03–2.04)	1.54 (1.20–1.97)

*Multivariable adjustment by age, gender, race/ethnicity, cohort, smoking status, BMI, and history of diabetes mellitus, in the entire study population.
†Multivariable adjustment by age, gender, cohort, smoking status, BMI, and history of diabetes mellitus, in white participants only.

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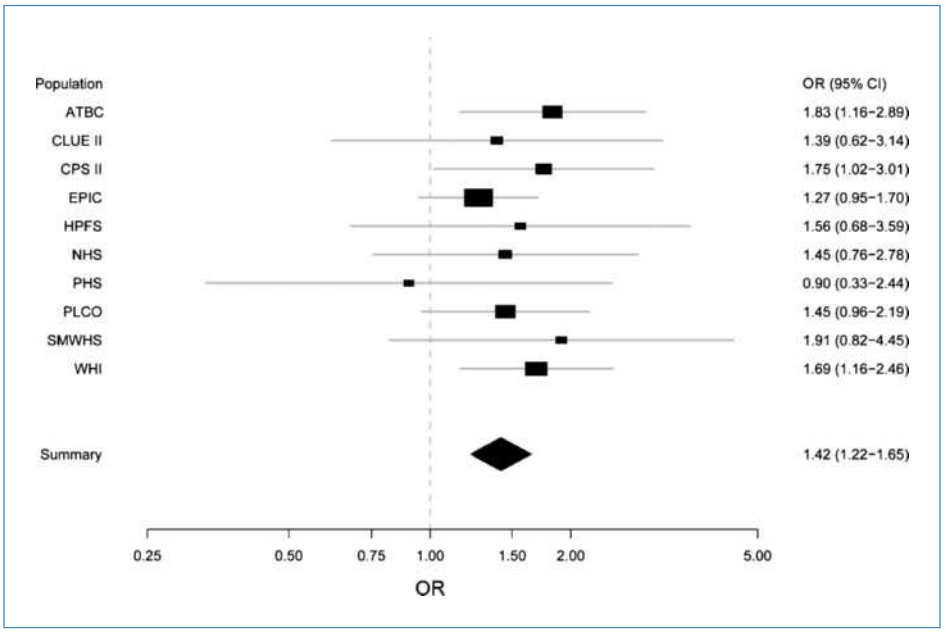

Figure 1. Risk of pancreatic cancer in non-O blood type versus O blood type by a prospective cohort study. Two participating cohorts (NYUWHS and WHS) were not included in this figure due to unstable estimates with small numbers of contributed subjects (≤25 cases).

blood type was concordant with laboratory-assessed serologic blood type in 91% of participants (14). We further examined the concordance of genotype-derived and self-reported blood type in 187 NHS and HPFS participants included in PanScan. In 92% of subjects, the self-reported blood type and the genotype-derived blood type were identical; this proportion is within the limit of error expected from the prior validation of self-report and strongly supports the accuracy of the genotype-defined blood group alleles.

Assessment of covariates. Across all 12 participating cohorts, covariates were collected through written questionnaires or in-person interviews. Detailed descriptions of data

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

Second allele	First allele		
	O	A	B
O			
No. of subjects	1,168	1,080	377
Age-adjusted OR	1.0	1.35 (1.14–1.59)	1.43 (1.14–1.81)
Multivariable-adjusted OR*	1.0	1.33 (1.13–1.58)	1.45 (1.14–1.85)
Multivariable-adjusted OR†	1.0	1.32 (1.11–1.57)	1.47 (1.14–1.90)
A			
No. of subjects	—	262	186
Age-adjusted OR		1.61 (1.23–2.11)	1.43 (1.05–1.95)
Multivariable-adjusted OR*		1.61 (1.22–2.18)	1.47 (1.07–2.02)
Multivariable-adjusted OR†		1.68 (1.27–2.24)	1.45 (1.03–2.04)
B			
No. of subjects	—	—	44
Age-adjusted OR			2.35 (1.26–4.39)
Multivariable-adjusted OR*			2.42 (1.28–4.57)
Multivariable-adjusted OR†			2.54 (1.19–5.39)

*Multivariable adjustment by age, gender, race/ethnicity, cohort, smoking status, BMI, and history of diabetes mellitus, in the entire study population.

†Multivariable adjustment by age, gender, cohort, smoking status, BMI, and history of diabetes mellitus, in white participants only.

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Table 5. ORs (95% CIs) and incidence rates for pancreatic cancer by genotype-derived ABO blood type and selected covariates among white participants

Predisposing factor	Genotype-derived ABO blood type		$P_{interaction}$
	O	Non-O	
Smoking status*			0.33
Never/quit date ≥5 y			
No. of cases/controls	241/357	433/449	
Adjusted OR† (95% CI)	1.0	1.44 (1.17–1.78)	
Incidence rate (cases/100,000 subjects)	24.5	35.3	
Current/quit date <5 y or unknown			
No. of cases/controls	136/150	355/263	
Adjusted OR† (95% CI)	1.66 (1.22–2.27)	2.68 (2.03–3.54)	
Incidence rate (cases/100,000 subjects)	40.7	65.6	
BMI			0.95
<25 kg/m^2			
No. of cases/controls	171/252	347/350	
Adjusted OR† (95% CI)	1.0	1.43 (1.11–1.83)	
Incidence rate (cases/100,000 subjects)	26.1	37.4	
≥25 kg/m^2			
No. of cases/controls	295/353	560/490	
Adjusted OR† (95% CI)	1.20 (0.93–1.54)	1.66 (1.31–2.10)	
Incidence rate (cases/100,000 subjects)	31.3	43.2	
History of diabetes mellitus			0.44
No			
No. of cases/controls	382/550	772/753	
Adjusted OR† (95% CI)	1.0	1.46 (1.24–1.73)	
Incidence rate (cases/100,000 subjects)	27.1	39.6	
Yes			
No. of cases/controls	50/35	75/50	
Adjusted OR† (95% CI)	2.15 (1.35–3.41)	2.29 (1.55–3.39)	
Incidence rate (cases/100,000 subjects)	58.1	62.0	

*Participants from HPFS, NHS, PHS, and WHS were matched on smoking status and, therefore, were excluded from the joint analyses with smoking status.

†Multivariable adjustment by age, gender, cohort, smoking status, history of diabetes mellitus, and BMI, excluding the covariate included in the joint analysis.

collection methods have been published previously (see Supplementary Table S1 for references). 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. Participant characteristics were examined for cases and controls, and by blood type among controls. We compared the distribution of blood type alleles in our study with the distributions seen in other comparable populations. We used unconditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for pancreatic cancer by ABO alleles, adjusted for age, gender, race/ethnicity, cohort, smoking status, BMI, and history of diabetes. We then repeated our analyses, now limiting to white subjects and excluding the 74 cases and their matched controls that were included in our prior analysis of self-reported ABO serotype and pancreatic cancer risk (14). In addition, to adjust for detectable differences in population substructure, a principal component analysis of all DNA samples used in PanScan was performed using the entire set of the ~550,000 SNPs with the EIGENSTRAT program (15, 18). Five principal components were effective for distinguishing significant population groups, and we performed an additional analysis that included these principal components in our models to correct for genetic admixture. We used the likelihood ratio test for nested models to assess whether a model based on ABO genotypes improved model fit relative to a model using rs505922 alone.

We assessed effect-measure modification by conducting analyses stratified by other risk factors for pancreatic cancer, including age (≤65, 66–75, >75 years), gender (male, female), race/ethnicity (white, nonwhite), smoking (current/recent quitter, never/distant quitter), and BMI (<25, 25–29.9, >30

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kg/m^2). Tests for modification by other risk factors were assessed by entering the cross-product of blood type and the covariate into the model. We jointly assessed the effect of the ABO genotype on pancreatic cancer risk and the three best-characterized modifiable risk factors for pancreatic cancer: tobacco use, obesity, and diabetes mellitus. Participants from the HPFS, NHS, PHS, and WHS were matched on smoking status and, therefore, were excluded from the joint analyses with smoking status.

The population attributable fraction (PAF) for pancreatic cancer due to non-O blood groups was calculated using the following equation: PAF = Pd [(OR − 1) / OR], where Pd is the prevalence of exposure among pancreatic cancer cases and OR is the multivariable-adjusted OR calculated by logistic regression models (19). Using the PAF and population average incidence rate λ, we calculated the absolute incidence rates of pancreatic cancer in whites by ABO blood group G as (1 − PAF) λ OR_G (20). Average age-adjusted population rates weighted by gender for U.S. whites 50 years and older were obtained from the Surveillance, Epidemiology, and End Results data.

We assessed heterogeneity in the association between blood type and pancreatic cancer risk across the cohorts using Cochran's *Q* statistic (21). All statistical analyses were performed using the SAS 9.1 statistical package (SAS Institute), and all *P* values were two-sided.

Results

From the 12 participating cohorts, 1,534 pancreatic cancer cases and 1,583 controls were available for analysis. As expected, a higher proportion of cases than controls were current smokers or reported a history of diabetes (Supplementary Table S2). Characteristics of control participants were similar among the ABO blood types, except that participants with blood types AB and B were less likely to be white, a pattern consistent with the increased frequency of B alleles among Asians (Table 1). The frequency distributions of ABO alleles were highly similar among our control participants and subjects in previous studies (Table 2; refs. 14, 16, 22–25). The frequencies of blood types O, A, AB, and B were 41.5%, 40.6%, 5.6%, and 12.3%, respectively, among our control participants, which were also consistent with previously reported studies (14, 16, 22–25).

We estimated the risk of pancreatic cancer according to genotype-derived ABO blood type among all study participants (Table 3). Compared with subjects with blood type O, those with blood types A, AB, and B were at greater risk of developing pancreatic cancer. Moreover, when we limited the analysis to whites only (Table 3), removed the 74 cases and matched controls who were included in a previous analysis of self-reported ABO blood type and pancreatic cancer risk (14), or included the five principal components of genetic structure in our model, the adjusted ORs for blood types A, AB, and B were essentially unchanged. The incidence rates for pancreatic cancer (cases per 100,000 persons at risk) among white participants with blood types O, A, AB, and B were 28.9, 39.9, 41.8, and 44.5, respectively.

We further examined pancreatic cancer risk according to the ABO genotype. An increased risk was observed with the addition of each non-O allele (OR, 1.29; 95% CI, 1.16–1.42). Compared with subjects with OO, those with AO and AA had ORs of 1.33 (95% CI, 1.13–1.58) and 1.61 (95% CI, 1.22–2.18), respectively, whereas subjects with BO and BB had ORs of 1.45 (95% CI, 1.14–1.85) and 2.42 (95% CI, 1.28–4.57), respectively (Table 4). The comparison of a model including full genotypic variability at the ABO locus and a model with only genotypic variation at rs505922, the most statistically significant SNP from the GWAS, resulted in a *P* value of 0.48.

We calculated the PAF for participants with non-O blood groups (i.e., blood types A, AB, or B). White participants with non-O blood group had an adjusted OR for pancreatic cancer of 1.42 (95% CI, 1.21–1.66). Based on this OR and the prevalence of non-O blood types in these cases (66.2%), 19.5% of all pancreatic cancers in our European ancestry population were attributable to the inheritance of a non-O blood group.

The ORs comparing subjects with non-O blood groups to those with blood group O were highly similar across cohorts [Cochran's *Q* statistic *P* = 0.91 for the comparison of non-O blood type (i.e., A, AB, or B) to O blood type across cohorts; Fig. 1]. In addition, the ORs comparing subjects with non-O blood groups to those with blood group O were not modified to a significant extent by age, gender, race/ethnicity, smoking status, or BMI (Supplementary Table S3). As tobacco use, obesity, and diabetes mellitus are the best-defined modifiable risk factors for pancreatic cancer, we also evaluated these covariates and ABO blood type in joint models (Table 5). In combination with smoking, overweight, or diabetes, the non-O blood type was associated with ORs of 2.68, 1.66, and 2.29, respectively, compared with subjects who had O blood type and lacked the exposure. These ORs are compatible with a multiplicative OR model for the joint effects of these factors and non-O blood type; there was no evidence for statistically significant interactions.

Discussion

Among pancreatic cancer cases and controls from 12 large prospective cohort studies, we observed a significantly elevated risk for incident pancreatic cancer among those with blood group alleles A or B compared with those with blood group O. Importantly, an increased risk was noted with the addition of each non-O allele, with a large increase in risk noted for participants with blood type BB. These data suggest that additional useful risk information may be provided by determining the full genotypic variability at the ABO locus; however, further studies are needed of ABO alleles and pancreatic cancer risk to confirm these findings. Joint models showed further increases in risk when ABO status was evaluated jointly with known risk factors for pancreatic cancer; statistically significant interactions were not observed between known predisposing factors and ABO blood type, indicating that this risk factor

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may be relevant across populations with diverse clinical characteristics. We estimate that 19.5% of all cases of pancreatic cancer in European ancestry populations are attributable to inheriting a non-O blood group.

Studies examining serotype-defined blood type or tumoral expression of ABO antigens have suggested a role for ABO blood groups in the development and progression of cancer for several decades (26). However, studies examining serologic blood type and pancreatic cancer risk have been somewhat inconsistent (9–13), likely due to small case numbers, retrospective data collection, heterogeneous pathology review, and the use of poorly matched control populations.

We previously performed a prospective cohort study of participants in the NHS and HPFS to examine the influence of serologic-defined ABO blood type on the subsequent development of pancreatic cancer (14). Compared with participants with blood group O, those with blood groups A, AB, or B were more likely to develop pancreatic cancer, with adjusted hazard ratios for incident pancreatic cancer of 1.32 (95% CI, 1.02–1.72), 1.51 (95% CI, 1.02–2.23), and 1.72 (95% CI = 1.25–2.38), respectively. However, this analysis included only 316 pancreatic cancer cases and was unable to examine the full range of blood type allelic variation (i.e., OO, AO, AA, AB, BO, and BB), as it was based on serotype.

Cases and controls in the current analysis were drawn from the Pancreatic Cancer Cohort Consortium, which recently completed a GWAS involving ~550,000 SNPs across the human genome (15). The GWAS identified four SNPs at the *ABO* gene locus (rs505922, rs495828, rs657152, and rs630014) as among the most statistically significant associations with pancreatic cancer risk ($P < 10^{-5}$); however, the mechanism by which these SNPs influence risk is unknown. A possible explanation for the association of these SNPs with disease risk is their linkage to ABO glycosyltransferase specificity, i.e., with the polymorphisms that define glycosyltransferases O, A, and B. The current study would support this explanation, given the increase in cancer risk with increasing the number of non-O alleles, and the suggested differences in risk for subjects with blood types AA and BB. Alternatively, SNPs at the ABO locus could modulate gene expression, such that glycosyltransferase specificity is of lesser importance than levels of *ABO* gene expression. Finally, our study cannot rule out that these SNPs may act as markers of allelic variants in nearby genes, and the ABO antigens may not be directly involved in pancreatic carcinogenesis.

Glycoconjugates are important mediators of intercellular adhesion and membrane signaling, two processes integral to malignant progression and spread (7). In addition, these surface molecules are recognized by the host immune response and may have a role in facilitating immunosurveillance for malignant cells (27). Nevertheless, little data are available to directly link these processes to an association between blood type and pancreatic cancer risk.

Chronic inflammation is a predisposing factor for pancreatic carcinogenesis; pancreatic cancer induces a strong desmoplastic reaction that acts as an abundant source of inflammatory mediators, supporting tumor growth and metastases (28, 29). Interestingly, two recent GWAS suggest that ABO blood group antigens may affect the systemic inflammatory state (16, 30). SNPs at the ABO locus were associated with two serum markers of inflammation—tumor necrosis factor-α (TNF-α; ref. 30) and soluble intercellular adhesion molecule 1 (16). TNF-α is a proinflammatory cytokine known to modulate rates of pancreatic ductal cell apoptosis (28), whereas plasma levels of soluble intercellular adhesion molecule 1 are associated with the risk of incident diabetes (31), a known predisposing factor for pancreatic cancer. These results raise the possibility that blood group antigens may alter the systemic inflammatory state, thereby influencing the risk of developing pancreatic cancer.

Our study has several possible limitations. Blood type in this study was derived from genotype data not determined serologically, leading to the possibility of measurement error and exposure misclassification. However, the *ABO* gene was cloned ~20 years ago (4, 5), and methods for determining blood type from a subject's DNA are well established (22, 24, 25). In addition, the genotype-derived blood types imputed in the current study were highly concordant with validated blood type in NHS and HPFS participants. Moreover, any resultant misclassification due to measurement error is likely to be nondifferential in nature, and therefore attenuates, rather than exaggerates, 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 association between ABO blood type and risk did not differ materially between the white and nonwhite subjects in this study. Nonetheless, further investigations that include more diverse study populations are warranted. Finally, we cannot definitively rule out the presence of residual confounding or that our risk estimates are higher than those that will be confirmed in other populations due to the winner's curse (32).

Our study has several notable strengths. The Pancreatic Cancer Cohort Consortium 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 (33, 34). In addition, after adjusting for potential population stratification bias by including the top five principal components of genetic variation as covariates in the logistic regression models, our results were unchanged. Finally, prospectively collected covariate information was not subject to recall bias or the need for proxy interviews and, thus, improved our ability to control for confounding and evaluate effect modification.

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There remains only a limited understanding of the genetic determinants of pancreatic cancer risk. Our results suggest that ABO blood group alleles represent a common, partially penetrant genetic determinant for pancreatic cancer. Additional investigation is necessary to elaborate mechanisms by which ABO antigens may influence pancreatic cancer risk. In the future, it is possible that the ABO blood type could be incorporated into predictive models for this disease, together with other genetic loci and currently identified risk factors, such as tobacco use, obesity, and diabetes mellitus.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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