Research Article

Cancer Epidemiology, Biomarkers & Prevention

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

Brian M. Wolpin[1,2], Peter Kraft[3,4], Mousheng Xu[3], Emily Steplowski[5], Martin L. Olsson[6], Alan A. Arslan[7,8], H. Bas Bueno-de-Mesquita[9,10], Myron Gross[11], Kathy Helzlsouer[12,13], Eric J. Jacobs[14], Andrea LaCroix[15], Gloria Petersen[16], Rachael Z. Stolzenberg-Solomon[17], Wei Zheng[18], Demetrius Albanes[18], Naomi E. Allen[19], Laufey Amundadottir[18,20], Melissa A. Austin[21], Marie-Christine Boutron-Ruault[22], Julie E. Buring[23,24], Federico Canzian[25], Stephen J. Chanock[18,21], J. Michael Gaziano[26], Edward L. Giovannucci[2,3,27], Göran Hallmans[28], Susan E. Hankinson[2,3], Robert N. Hoover[18], David J. Hunter[2,3], Amy Hutchinson[18,29], Kevin B. Jacobs[18,30], Charles Kooperberg[16], Julie B. Mendelsohn[18], Dominique S. Michaud[3,30], Kim Overvad[31], Alpa V. Patel[15], Maria-José Sanchéz[32], Leah Sansbury[33], Xiao-Ou Shu[19], Nadia Slimani[34], Geoffrey S. Tobias[18], Dimitrios Trichopoulos[3,35], Paolo Vineis[36], Kala Visvanathan[14], Jarmo Virtamo[37], Jean Wactawski-Wende[38], Joanne Watters[34], Kai Yu[18], Anne Zeleniuch-Jacquotte[8,9], Patricia Hartge[18], and Charles S. Fuchs[1,2]

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.

Authors' Affiliations: [1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; [2]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; [4]Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts; [5]Information Management Services, Silver Spring, Maryland; [6]Division of Hematology & Transfusion Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden; [7]Department of Obstetrics and Gynecology, New York University School of Medicine, New York; [8]Department of Environmental Medicine, New York University School of Medicine, New York; [9]New York University Cancer Institute, New York; [10]National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands; [11]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, the Netherlands; [12]Department of Laboratory Medicine/Pathology, School of Medicine, University of Minnesota, Minneapolis, Minnesota; [13]Prevention and Research Center, Mercy Medical Center, Baltimore, Maryland; [14]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health and Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; [15]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia; [16]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; [17]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; [18]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; [19]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee; [20]Cancer Epidemiology Unit, University of Oxford, Oxford, UK; [21]Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; [22]Department of Epidemiology and Institute for Public Health Genetics, School of Public Health, University of Washington, Seattle, Washington; [23]Inserm (Institut National de la Santé et de la Recherche Médicale) and Institut Gustave Roussy, Villejuif, France; [24]Divisions of Preventive Medicine and Aging, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Maryland; [25]Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, Maryland; [26]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [27]Physicians' Health Study, Divisions of Aging, Cardiovascular Medicine, and Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, and Massachusetts Veterans Epidemiology Research and Information Center, Veterans Affairs Boston Healthcare System, Boston, Maryland; [28]Department of Nutrition, Harvard School of Public Health, Boston, Maryland; [29]Department of Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden; [30]Core Genotyping Facility, SAIC-Frederick Inc., NCI-Frederick, Frederick, Maryland; [31]Division of Epidemiology, Public Health and Primary Care, Imperial College, London, UK; [32]Department of Epidemiology, School of Public Health, Aarhus University, Aalborg, Denmark; [33]Andalusian School of Public Health and CIBER de Epidemiologia y Salud Publica (CIBERESP), Spain; [34]Division of Cancer Control and Population Science, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; [35]International Agency for Research on Cancer, Lyon, France; [36]Bureau of Epidemiologic Research, Academy of Athens, Greece; [37]MRC-HPA Centre for Environment and Health, School of Public Health, Imperial College, London, UK; [38]Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; and [39]Department of Social and Preventive Medicine, University at Buffalo, SUNY, Buffalo, New York

Note: A.A. Arslan, H. Bas Bueno-de-Mesquita, M. Gross, K. Helzlsouer, E. J. Jacobs, A. LaCroix, G. Petersen, R.Z. Stolzenberg-Solomon, and C.S. Fuchs are Steering Committee members. Senior authors P. Hartge and C. S. Fuchs contributed equally.

Corresponding Author: Brian Wolpin, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115. Phone: 617-632-6942; Fax: 617-632-5370. E-mail: bwolpin@partners.org

doi: 10.1158/1055-9965.EPI-10-0751

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

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.

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.

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

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.

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.

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.

Grant Support

The funding sources for this study did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

The NYU Women's Health Study is supported by research grants R01CA034588, R01CA098661, center grant P30CA016087 from the NCI, and the center grant ES000260 from the National Institute of Environmental Health Sciences.

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators is available. (54).

P.H.S. was supported by grants CA 97193, CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health.

The NHS, HPFS, and WHS at Harvard were supported by the National Cancer Institute, National Institutes of Health (Grants No. P01 CA87969, P01 CA55075, P50 CA127003, R01 CA124908). Brian Wolpin, MD, MPH, was supported by NCI K07 CA140790, an American Society of Clinical Oncology Career Development Award, and a Howard Hughes Medical Institute Early Career Physician-Scientist Award.

The Shanghai Men's Health Study was supported by the National Cancer Institute extramural research grant [R01 CA82729]. The Shanghai Women's Health Study was supported by the National Cancer Institute extramural research grant [R01 CA70867] and, partially for biological sample collection, by the Intramural Research Program of National Cancer Institute (Division of Cancer Epidemiology and Genetics).

We are in debt to the contributions of Drs. Yu-Tang Gao and Yong-Bing Xiang in these 2 cohort studies. The studies would not be possible without the continuing support and devotion from the study participants and staff of the SMHS and SWHS.

PLCO was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. The authors thank Drs. Christine Berg and Philip Prorok, Division of Cancer Prevention, National Cancer Institute, the Screening Center investigators and staff of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Mr. Tom Riley and staff, Information Management Services, Inc., Ms. Barbara O'Brien and staff, Westat, Inc., Mr. Tim Sheehy and staff, DNA Extraction and Staging Laboratory, SAIC-Frederick, Inc, and Ms. Jackie King and staff, BioReliance, Inc. Most importantly, we acknowledge the study participants for their contributions to making this study possible.

The ATBC Study was supported by U.S. Public Health Service contractsN01-CN-45165, N01-RC-45035, N01-RC-37004, and HHSN261201000006C from the National Cancer Institute, Department of Health and Human Services, and by funding from the Intramural Research Program of the National Cancer Institute.

For the EPIC cohorts, all coauthors coordinated the initial recruitment and management of the studies. All authors contributed to the final paper. The authors thank all of the participants who took part in this research and the funders and support and technical staff who made this study possible. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue contre le Cancer, Société 3M, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Medicale (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and Wellcome Trust (United Kingdom).

CLUE II was supported by National Institute of Aging grant (5U01AG018033) and National Cancer Institute grants (CA105069, CA73790). The authors express their appreciation to the participants of the CLUE II cohort and thank the staff at the George W. Comstock Center for Public Health Research and Prevention for their dedication and contributions to the study: Judy Hoffman-Bolton, Clara Krumpe, Kitty Spoonire, and Betty Miner.

The Cancer Prevention Study II Nutrition Cohort is supported by the American Cancer Society. The authors thank all of the men and women in the Cancer Prevention Study II Nutrition Cohort for their many years of dedicated participation in the study.

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U. S. Government.

Received 07/13/2010; accepted 10/01/2010; published OnlineFirst 10/22/2010.

References

1. Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol 2004;41:93–117.
2. Hakomori S. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. Biochim Biophys Acta 1999;1473:247–66.
3. Wolpin BM, Chan AT, Hartge P, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst 2009;101:424–31.
4. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet 2009;41:986–90.

5. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst 2010;102:502–5.
6. Wolpin BM, Kraft P, Gross M, et al. Pancreatic cancer risk and ABO blood group alleles: results from the Pancreatic Cancer Cohort Consortium. Cancer Res 2010;70:1015–23.
7. Yamamoto F, McNeill PD, Hakomori S. Human histo-blood group A2 transferase coded by A2 allele, one of the A subtypes, is characterized by a single base deletion in the coding sequence, which results in an additional domain at the carboxyl terminal. Biochem Biophys Res Commun 1992;187:366–74.
8. Storry JR, Olsson ML. The ABO blood group system revisited: a review and update. Immunohematology 2009;25:48–59.
9. Olsson ML, Chester MA. Frequent occurrence of a variant O1 gene at the blood group ABO locus. Vox Sang 1996;70:26–30.
10. Calafell F, Roubinet F, Ramirez-Soriano A, Saitou N, Bertranpetit J, Blancher A. Evolutionary dynamics of the human ABO gene. Hum Genet 2008;124:123–35.
11. Ferrer-Admetlla A, Sikora M, Laayouni H, et al. A natural history of FUT2 polymorphism in humans. Mol Biol Evol 2009;26:1993–2003.
12. Kelly RJ, Rouquier S, Giorgi D, Lennon GG, Lowe JB. Sequence and expression of a candidate for the human Secretor blood group alpha (1,2)fucosyltransferase gene (FUT2). homozygosity for an enzyme-inactivating nonsense mutation commonly correlates with the non-secretor phenotype. J Biol Chem 1995;270:4640–9.
13. Svensson L, Petersson A, Henry SM. Secretor genotyping for A385T, G428A, C571T, C628T, 685delTGG, G849A, and other mutations from a single PCR. Transfusion 2000;40:856–60.
14. Kraft P, Cox DG, Paynter RA, Hunter D, De Vivo I. Accounting for haplotype uncertainty in matched association studies: a comparison of simple and flexible techniques. Genet Epidemiol 2005;28:261–72.
15. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 2006;38:904–9.
16. Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
17. Blumenfeld OO, Patnaik SK. Allelic genes of blood group antigens: a source of human mutations and cSNPs documented in the Blood Group Antigen Gene Mutation Database. Hum Mutat 2004;23:8–16.
18. Pare G, Chasman DI, Kellogg M, et al. 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.
19. Yip SP. Single-tube multiplex PCR-SSCP analysis distinguishes 7 common ABO alleles and readily identifies new alleles. Blood 2000; 95:1487–92.
20. Gassner C, Schmarda A, Nussbaumer W, Schonitzer D. ABO glycosyltransferase genotyping by polymerase chain reaction using sequence-specific primers. Blood 1996;88:1852–6.
21. Aird I, Lee DR, Roberts JA. ABO blood groups and cancer of oesophagus, cancer of pancreas, and pituitary adenoma. Br Med J 1960;1 (5180):1163–6.
22. Vogel F. Controversy in human genetics. ABO blood groups and disease. Am J Hum Genet 1970;22:464–75.
23. Newell GR, Gordon JE, Monlezun AP, Horwitz JS. ABO blood groups and cancer. J Natl Cancer Inst 1974;52:1425–30.
24. Annese V, Minervini M, Gabbrielli A, Gambassi G, Manna R. ABO blood groups and cancer of the pancreas. Int J Pancreatol 1990;6:81–8.
25. Vioque J, Walker AM. Pancreatic cancer and ABO blood types: a study of cases and controls. Med Clin (Barc) 1991;96:761–4.
26. Yamamoto F, Clausen H, White T, Marken J, Hakomori S. Molecular genetic basis of the histo-blood group ABO system. Nature 1990;345:229–33.
27. Yamamoto F, Marken J, Tsuji T, White T, Clausen H, Hakomori S. Cloning and characterization of DNA complementary to human UDP-GalNAc: Fuc alpha 1–2Gal alpha 1–3GalNAc transferase (histo-blood group A transferase) mRNA. J Biol Chem 1990;265:1146–51.
28. Saitou N, Yamamoto F. Evolution of primate ABO blood group genes and their homologous genes. Mol Biol Evol 1997;14:399–411.
29. Nossent AY, Van Marion V, Van Tilburg NH, et al. von Willebrand factor and its propeptide: the influence of secretion and clearance on protein levels and the risk of venous thrombosis. J Thromb Haemost 2006;4:2556–62.
30. Gallinaro L, Cattini MG, Sztukowska M, et al. A shorter von Willebrand factor survival in O blood group subjects explains how ABO determinants influence plasma von Willebrand factor. Blood 2008;111:3540–5.
31. Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr., Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood 1987;69:1691–5.
32. Wu O, Bayoumi N, Vickers MA, Clark P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. J Thromb Haemost 2008;6:62–9.
33. Tregouet DA, Heath S, Saut N, et al. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. Blood 2009;113:5298–303.
34. Morelli VM, de Visser MC, van Tilburg NH, et al. ABO blood group genotypes, plasma von Willebrand factor levels and loading of von Willebrand factor with A and B antigens. Thromb Haemost 2007; 97:534–41.
35. Chester MA, Olsson ML. The ABO blood group gene: a locus of considerable genetic diversity. Transfus Med Rev 2001;15:177–200.
36. Hosseini-Maaf B, Hellberg A, Rodrigues MJ, Chester MA, Olsson ML. ABO exon and intron analysis in individuals with the AweakB phenotype reveals a novel O1v-A2 hybrid allele that causes four missense mutations in the A transferase. BMC Genet 2003;4:17.
37. Thuresson B, Chester MA, Storry JR, Olsson ML. ABO transcript levels in peripheral blood and erythropoietic culture show different allele-related patterns independent of the CBF/NF-Y enhancer motif and multiple novel allele-specific variations in the 5′- and 3′-noncoding regions. Transfusion 2008;48:493–504.
38. Seltsam A, Hallensleben M, Kollmann A, Blasczyk R. The nature of diversity and diversification at the ABO locus. Blood 2003;102:3035–42.
39. Lindesmith L, Moe C, Marionneau S, et al. Human susceptibility and resistance to Norwalk virus infection. Nat Med 2003;9:548–53.
40. Ikehara Y, Nishihara S, Yasutomi H, et al. Polymorphisms of two fucosyltransferase genes (Lewis and Secretor genes) involving type I Lewis antigens are associated with the presence of anti-Helicobacter pylori IgG antibody. Cancer Epidemiol Biomarkers Prev 2001;10:971–7.
41. Ruiz-Palacios GM, Cervantes LE, Ramos P, Chavez-Munguia B, Newburg DS. Campylobacter jejuni binds intestinal H(O) antigen (Fuc alpha 1, 2Gal beta 1, 4GlcNAc), and fucosyloligosaccharides of human milk inhibit its binding and infection. J Biol Chem 2003;278:14112–20.
42. Magalhaes A, Gomes J, Ismail MN, et al. Fut2-null mice display an altered glycosylation profile and impaired BabA-mediated Helicobacter pylori adhesion to gastric mucosa. Glycobiology 2009; 19:1525–36.
43. Hazra A, Kraft P, Selhub J, et al. Common variants of FUT2 are associated with plasma vitamin B12 levels. Nat Genet 2008;40: 1160–2.
44. Tanaka T, Scheet P, Giusti B, et al. Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. Am J Hum Genet 2009;84:477–82.
45. O'Donnell J, Boulton FE, Manning RA, Laffan MA. Genotype at the secretor blood group locus is a determinant of plasma von Willebrand factor level. Br J Haematol 2002;116:350–6.
46. Schleef M, Strobel E, Dick A, Frank J, Schramm W, Spannagl M. Relationship between ABO and Secretor genotype with plasma levels of factor VIII and von Willebrand factor in thrombosis patients and control individuals. Br J Haematol 2005;128:100–7.
47. Melzer D, Perry JR, Hernandez D, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). Jt 2008;4:e1000072.
48. Paterson AD, Lopes-Virella MF, Waggott D, et al. 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;29:1958–67.
49. Qi L, Cornelis MC, Kraft P, et al. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. Hum Mol Genet 2010;19:1856–62.
50. Barbalic M, Dupuis J, Dehghan A, et al. Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. Hum Mol Genet 2010;19:1863–72.

51. Hezel AF, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev 2006;20:1218–49.

52. Wacholder S, Rothman N, Caporaso N. Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. J Natl Cancer Inst 2000;92:1151–8.

53. Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: II. Results for the global burden of disease 2000. BMC Cancer 2002;2:37.

54. Available from: http://www.whiscience.org/publications/WHI_investigators_shortlist.pdf.