

Relationship between ABO Blood Group Antigens and Pancreatic Cancer-Systemic Review

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Abstract

Pancreatic cancer is among the most aggressive types of cancer. It has mortality rates as the seventh most frequent cause of cancer death worldwide. The association between ABO blood group and risk of pancreatic cancer has been known for more than 40 years. Various studies, in detail, although conflicting on many occasions, on large population groups, cohort studies, case-control studies, retrospective comparative studies, and meta-analysis all provide a systematic knowledge on cancer and human ABO blood groups. Population studies were compared among pancreatic cancer cases and nested controls. All participants were selected according to certain routine factors to emphasize an important point in the selection of population controls. Studies showed statistically distinct distribution of blood groups in different regions and different ABO frequencies in those populations was studied and combined without introducing bias providing evidence of associations of cancer of the pancreas with the ABO blood groups. Evidence exists that there is an increased risk of pancreatic cancer among blood group B individuals and a modest excess risk for pancreatic cancer in blood group A individuals. pancreatic cancer susceptibility loci is identified in ABO gene. ABO blood group alleles represent a common, partially penetrant genetic determinant for pancreatic cancer. ABO blood group genes are mapped at 9q34.2 region in which genetic alteration is common in pancreatic cancer. The authors of various studies suggested a role of ABO glycosyltransferase specificity in pancreatic tumorigenesis. The hypothesis that ABO glycosyltransferase activity influences pancreatic cancer risk was simultaneously confirmed by many. GWAS (genome-wide association study) identified pancreatic cancer susceptibility loci in the ABO gene and an increase in risk was noted with the addition of each non-O allele, thus supporting earlier epidemiological evidence that people with blood group O may have a lower risk of pancreatic cancer than those with groups A, B or AB. Future studies should examine the mechanism linking pancreatic cancer risk to ABO blood group.

Keywords- ABO Blood group, pancreatic adenocarcinoma, glycosyltransferase, risk factor, genome.

INTRODUCTION

In India, cancer has become one of the leading causes of death. The association between inherited blood group and the risk of various malignancies has been dealt with in detail by many authors, reasons being, ABO blood groups are a stable feature of population and they differ among various groups. Various studies, in detail, on large population groups, cohort studies, case-control studies, and meta-analysis all provide a systematic knowledge on cancer and human ABO blood groups.

In the early 20th century Dr. Karl Landsteiner identified three blood groups⁽³⁰⁾. A single gene on chromosome 9q34 and its nucleotide sequence, found to define a person's blood group, was elucidated in 1990^(48,49). The ABO gene encodes a glycosyltransferase with three main variant alleles (A, B, and O), with different substrate specificities⁽³⁴⁾. 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⁽¹⁸⁾.

In laboratory investigations, patient-derived pancreatic cancer cells have different patterns of expression of blood group antigens on their cell surface than cells in adjacent normal pancreatic ducts^(24,39), suggesting that modifications to glycosyltransferase specificity occur during pancreatic tumorigenesis. Alterations in surface glycoconjugates thought to lead to modifications in intercellular adhesion, membrane signaling, and

immunosurveillance, that influence tumor development and spread^(51,37).

Human pancreatic cancer has shown to express either A or B antigens corresponding to the individual blood group⁽¹¹⁾ or lose blood group antigen expression⁽¹⁰⁾. Deletion of A, B, H or Lewis antigens and incompatible expression of A or B antigens were seen as cancer-associated in the pancreas⁽²³⁾. Incompatible expression of blood group-related antigens was observed in pancreatic cancer cells, compared with patient blood group type, indicating that Lewis antigen expression in pancreatic cancer independent of the blood group phenotype and may be useful as a tumor marker⁽³³⁾.

A correlation of blood group antigen expression in tumors with metastasis and prognosis had been reported for various human malignancies and the loss or presence of human blood group antigens can increase the expression of certain blood group carbohydrate antigens on the surface of cancer cells that can be useful prognostic and diagnostic markers as is the appearance and disappearance of blood type antigen hallmarking malignancies.

HISTORY

The relationship between ABO blood group and risk of pancreatic cancer has been known for more than 4 decades, and yet has received little attention. In 1960, Aird et al. carried out a study in the United Kingdom and detected "evidence of some strength that cancer of the pancreas is commoner in persons of group A than in persons of groups

O or B"⁽¹⁾. Four years later, Macafee showed "a deficiency of blood group A and an excess of blood group B when compared with the controls"⁽²⁷⁾. Thirty years later, a study in Italy confirmed an increased risk of pancreatic cancer among blood group B individuals⁽³⁾.

Nearly contemporarily, a six-country hospital-based case-control study observed a moderate excess risk for pancreatic cancer in blood group A individuals⁽⁴⁰⁾.

After the conflicting results of the aforementioned studies, several recent reports establishing an association between ABO blood group and pancreatic cancer have reinstated the interest in this relation.^(2,36,41-43)

A cohort study in, 2010, USA found that, "compared to individuals with blood group O, patients with non-O blood group were more likely to develop pancreatic cancer"⁽⁴¹⁾. Simultaneously, in 2010, the multinational Pancreatic Cancer Cohort Consortium (PanScan) I GWAS identified pancreatic cancer susceptibility loci in the ABO gene⁽²⁾; and a combined analysis supported earlier epidemiological evidence that "people with blood group O may have a lower risk of pancreatic cancer than those with groups A, B or AB". In 2010, the influence of specific ABO genotypes on pancreatic cancer risk was assessed by Wolpin et al., suggesting the role of ABO glycosyltransferase specificity in pancreatic tumorigenesis and showed that A1 allele confers greater pancreatic cancer risk than A2 allele⁽⁴³⁾.

The association of pancreatic cancer with the A allele was predominantly due to A1 glycosyltransferase, which had greater activity than A2 glycosyltransferase⁽²⁹⁾, a fact that was recently confirmed by a large multicentre study in the context of the PANcreatic Disease ReseArch

(PANDoRA) consortium⁽³⁶⁾, showing that only carriers of the A allele had increased risk of the disease, while carriers of the B allele did not

have. The relevance of the ABO blood group and *H. pylori* infection for the development of pancreatic cancer was recently analysed in 2010 by Risch and colleagues⁽³⁵⁾, reporting that the increased risk of pancreatic cancer among the individuals with non-O blood group was even higher if they were also seropositive for CagA-negative *H. Pylori*.

Assessment of ABO blood group alleles

Subjects with non-O ABO blood group alleles had increased risk of pancreatic cancer. Glycosyltransferase activity was greater for the A1 versus A2 variant, whereas O01 and O02 variants were non-functioning⁽⁴⁴⁾. ABO blood group subtype alleles and secretor status were examined for cases and controls, and the distribution of blood type alleles in the study was compared with that seen in other comparable populations. Age-adjusted and multivariable-adjusted ORs (Odds Ratio) for incident pancreatic cancer by number of blood group subtype alleles were calculated using logistic regression.

Another study showed that each subject has two ABO alleles, six genotypes were possible: OO, AO, AA, AB, BO, and BB. Age-adjusted and multivariable-adjusted ORs (95% CIs) for incident pancreatic cancer by genotype-derived ABO blood type assessed risk of pancreatic cancer in non-O blood type versus O blood type by a prospective cohort study⁽⁹⁾.

The association of blood type and risk of pancreatic cancer was studied in the context of two prospective cohort studies. Cox proportional hazards models were used to calculate the risk of pancreatic cancer by blood type after adjustment for other known risk factors⁽⁸⁾.

At the various centres listing all cases of cancer of the pancreas that had been blood-grouped were included. It was possible that some of these may have been carcinomas of the ampulla of Vater or of the lower end of the common bile-duct, for when these advanced and spread into the pancreas it was not always possible to distinguish their precise anatomical origin. Distinctly different ABO frequencies in the population was studied and combined without introducing bias providing evidence of associations of cancer of the pancreas with the ABO blood groups⁽²¹⁾.

Studies showed statistical distribution of blood group in Germany and for German patients with pancreatic cancer, observing blood group O in 43 (25.9%) patients, blood group A in 94 (56.6%) patients, blood group B in 16 (9.6%) patients and blood group AB in 13 (7.8%) patients. Further was observed the positive rhesus antigen in 131 (78.9%) patients and the negative rhesus antigen in 35 (21.1%) patients. The Rhesus factor had no significant impact on the ABO-distribution⁽³²⁾.

Other genomic associations with pancreatic cancer were derived upon by studies conducted on SNPs from the two different studies original GWAS

(genome-wide association study) and PanScanII that were combined, resulting in data on individuals with pancreatic cancer and controls identifying three new genomic regions on chromosomes 13q22.1, 1q32.1 and 5p15.33 associated with an increased risk of pancreatic cancer⁽²⁵⁾.

Proportions of ABO blood groups for pancreatic cancer cases and regional blood donors were compared and the OR of the ABO blood group distribution of the pancreatic cancer patients in comparison with the ABO groups of the unique blood donors to the Central Blood Bank in the Pittsburgh area provided information to estimate the ABO frequencies in a local area⁽¹⁷⁾.

Relative incidence of carcinoma of the pancreas as comparisons of ABO distributions between patients and controls showed significant difference between the observed and expected distributions⁽²⁸⁾.

POPULATION STUDIES

ABO blood group subtype alleles (A) and secretor status (B) among pancreatic cancer cases and nested controls in 12 prospective cohort studies, (Single nucleotide polymorphism (SNP) data collected in the PanScan genome-wide association study were used to define blood group subtype alleles and secretor phenotype)^(3,45). 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. One control was selected per case within each cohort.

All cohort studies selected participants according to certain routine factors. Each cohort study selected participants with blood or buccal cells collected prior to cancer diagnosis⁽⁴⁶⁾. Incident pancreatic cancer cases identified by

self-report, report of next-of-kin or through national death indices, linkage with a cancer registry, or both, without prior knowledge of genetic data. 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.

The Pancreatic Cancer Cohort Consortium includes nested case-control studies from 12 prospective cohorts. ABO genotypes (OO, AO, AA, AB, BO, and BB) in 1,534 cases and 1,583 controls from 12 prospective cohorts in PanScan, was determined, grouping participants by genotype-derived serologic blood type (O, A, AB, and B). 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. All subjects with non-exocrine pancreatic tumors were excluded. All participants were selected according to certain routine factors. One control was selected per case within each cohort. Controls were matched according to certain routine factors. Controls were alive without pancreatic cancer on the incidence date of the matched case. Four cohorts were additionally matched on smoking status 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⁽⁹⁾.

The relationship between ABO blood type and the risk of incident pancreatic cancer in two large, independent, prospective cohort studies (the Nurses' Health Study and Health Professionals Follow-up Study) was separately examined, collecting blood group data on 107 503 US health professionals, with adjustment for other known risk factors, including age, tobacco use, body mass index, physical activity, and history of diabetes mellitus. All statistical tests were two-sided.⁽⁸⁾ The Nurses' Health Study (NHS) began in 1976 and completed a baseline questionnaire. Subsequently, participants have completed a self-administered, mailed questionnaire biennially to update information on their lifestyle, medical history, and diet. The Health Professionals Follow-up Study (HPFS) began in 1986 and completed a baseline questionnaire. This information was then updated with biennial questionnaires. In 1996, questionnaires in both cohorts were expanded to include ABO blood type and Rh type.

Another study showed control series of samples being used including 10 different hospitals, from Birmingham, Bristol, Cardiff, Leeds, Liverpool, London, Manchester, Newcastle, Oxford, Sheffield, and Scotland. Those for Birmingham, Cardiff, Liverpool, and Sheffield are enlarged samples. At five centres, however—namely, Bristol, Manchester, Newcastle, Glasgow, and Leeds—entirely new samples have been substituted for those previously used deliberately, to emphasize an important point in the selection of population controls.⁽²¹⁾

Patients from a select German population who underwent a resection of PC were evaluated in a period between 2000 and 2010⁽³²⁾. All patients suffered from histologically confirmed pancreatic cancer. Blood type assay from 166

patients (ABO antigen and Rhesus antigen) were conducted. As reference cohort, healthy blood donors were tested, whose blood types showed the same distribution as the reference distribution of the German population. Reference distribution was given as: blood group O 41%; blood group A 43%; blood group B 11%; blood group AB 5%; Rhesus antigen positive 85% and Rhesus antigen negative 15%.

The Panscan consortium (which consists of the Pancreatic Cancer Cohort Consortia and the Pancreatic Cancer Case-Control Consortia (Panc4)) performed a genome-wide association study (GWAS) with approximately 550,000 single nucleotide polymorphisms (SNPs) comparing 1,896 individuals with pancreatic cancer and 1,939 controls ascertained from 12 cohort studies and the Mayo clinic case-control study (PanScanI)⁽⁴⁾. The SNP variants that provided the strongest evidence of association were then validated in an independent set of 2,457 cases and 2,654 controls from eight case-control studies. In this work, several common variants at the ABO blood group locus showed significant evidence of association with pancreatic cancer in the combined data⁽¹⁵⁾.

One study investigated the relationship of pancreatic cancer incidence with ABO blood group in our Western Pennsylvania regional population compared the serologically-determined ABO blood group of pancreatic cancer patients with the ABO group of greater than 700 000 blood donors to the Central Blood Bank in Pittsburgh. Pancreatic cancer patients from the University of Pittsburgh's affiliated hospitals who had provided informed consent to be part of their pancreatic cancer research registry were included in a study⁽¹⁷⁾.

Another study showed data derived from the case records of 119 in-patients who were treated for carcinoma of the pancreas in the Belfast hospitals during an eight-year period, 1953-1960 inclusive. The patients and blood donor controls were drawn from the same population. The ABO blood group distribution was known for a large series⁽³²⁾ of current blood donors normally resident in the County.

DISCUSSION

Studies on the hypothesis that ABO glycosyltransferase activity influences pancreatic cancer risk rather than actions of other nearby genes on chromosome 9q34 showed an increased risk observed in participants with A1 but not A2 alleles. Compared with subjects with genotype O/O, genotypes A2/O, A2/A1, A1/O, and A1/A1 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⁽⁴⁶⁾. Among participants in a large prospective cohort consortium, ABO allele subtypes corresponding to increased glycosyltransferase activity were associated with increased pancreatic cancer risk.

From the 12 participating cohorts, study on pancreatic cancer cases and controls were available for analysis. As expected, a higher proportion of cases than controls were current smokers or reported a history of diabetes. 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. The frequency distributions of ABO alleles were highly similar among control participants and subjects in previous studies^(6,12,14,31,47,50). The frequencies of blood types O, A, AB, and B were 41.5%, 40.6%, 5.6%, and 12.3%, respectively, among control participants, which were also consistent with previously reported studies^(6,12,14,31,47,50) estimating the risk of pancreatic cancer according to genotype-derived ABO blood type among all study participants. Compared with subjects with blood type O, those with blood types A, AB, and B were at greater risk of developing pancreatic cancer⁽⁷⁾. A significantly elevated risk for incident pancreatic cancer among those with blood group alleles A or B compared with those with blood group O was observed. 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. During extended person-years of follow-up in two large, independent, prospective cohort studies ABO blood type was associated with the risk of developing pancreatic cancer ($P = .004$; log-rank test). Compared with participants with blood group O, those with blood groups A, AB, or B were more likely to develop pancreatic cancer (adjusted hazard ratios for incident pancreatic cancer were 1.32 [95% confidence interval {CI} = 1.02 to 1.72], 1.51 [95% CI = 1.02 to 2.23], and 1.72 [95% CI = 1.25 to 2.38], respectively). The association between blood type and pancreatic cancer risk was nearly identical in the two cohorts (P interaction = .97). The age-adjusted incidence rates for pancreatic cancer per 100 000 person-years were 27 (95% CI = 23 to 33) for participants with blood type O, 36 (95% CI = 26 to 50) for those with blood type A, 41 (95% CI = 31 to 56) for those with blood type AB, and 46 (95% CI = 32 to 68) for those with blood type B⁽⁸⁾. Statistically significantly elevated risk for incident pancreatic cancer among participants with blood group antigens A or B compared with those with blood group O was observed. The highest risk was observed for participants with blood group B, and intermediate risks were observed for those with blood groups A and AB. The association between blood group and pancreatic cancer risk was not statistically significantly modified by other known risk factors for pancreatic cancer, including age, sex, smoking status, BMI, or physical activity. Within the combined cohorts, 17% of all cases of pancreatic cancer were attributable to inheriting a non-O blood group (blood groups A, B, or AB).

At the various centres that listed all cases of cancer of the pancreas that had been blood-grouped there was evidence of some strength that cancer of the pancreas is commoner in persons of group A than in persons of groups O or B. The evidence was rather more than suggestive. If ultimately confirmed, indicated a highly interesting finding because of the known relationship between diabetes and carcinoma of the pancreas. It is a known fact that carcinoma of the pancreas is commoner in diabetics than in non-diabetics, and it has appeared that blood group A is possibly commoner in diabetics than in the general population⁽²¹⁾.

Compiled evidence of association of ABO blood groups and Pancreatic cancer⁽¹⁵⁾ showed a definite correlation being established between ABO blood group and pancreatic cancer, which is among the most aggressive types of cancer.

Wolpin, 2009 Prospective cohort study showed Non-O blood group was associated with an increased risk of PC (adjusted HR 1.44; 95% CI: 1.14-1.82)

Amundadottir, 2009 Case-control study (GWAS) showed a significant association reported for rs505922, a single-nucleotide polymorphism, which maps to the first intron of the ABO gene. A multiplicative per-allele OR of 1.20 (95% CI: 1.12-1.28) supported earlier evidence that people with blood group O may have a lower risk of PC than those with groups A, B or AB

Wolpin, 2010 Case-control study showed an increased risk of PC noted with the addition of each non-O allele. Compared with the OO genotype, subjects with AO and AA genotypes had OR 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 OR of 1.45 (95% CI: 1.14-1.85) and 2.42 (95% CI: 1.28-4.57)

Iodice, 2010 Meta-analysis study showed the risk of PC was significantly decreased in O blood group (summary RR, 0.79; 95% CI, 0.70-0.90)

Risch, 2010 Case-control study showed the increased risk of PC among the individuals with non-O blood group was even higher if they were also seropositive for CagA-negative *H. pylori* (OR: 2.78; 95% CI: 1.49-5.20)

The incidence of pancreatic cancer in Germany was significantly associated with the ABO-blood group system. More patients with blood group A suffer from pancreatic cancer ($p < 0.001$) whereas blood group O was less frequently observed in patients with pancreatic cancer ($p < 0.001$). Genetic variations in the ABO locus of 9q34 may influence the pancreatic carcinogenesis and increase the risk for patients with blood group A and tapering the risk for patients with blood group O⁽³²⁾. The median age was 62 (34–82) years. The gender distribution favours male patients with a percentage of 56% male patients to 44% female patients.

Results of the first pancreatic cancer GWASs (genome-wide association studies) have added to knowledge of genetic loci associated with pancreatic cancer as well as the PanScan GWAS, a robust study that included a large number of cases and controls, many of whom were originally enrolled in large, well-designed prospective studies. Combined SNPs from the two studies identified three new genomic regions on chromosomes associated with an increased risk of pancreatic cancer⁽²⁵⁾. The two recent genome-wide association studies of pancreatic cancer have identified associations between pancreatic cancer risk and genetic variants in the ABO blood group gene, the locus containing the telomerase reverse transcriptase (hTERT) gene, the nuclear receptor family gene NR5A2 and a non-genic region on chromosome 13q22.1.

A case control study (2001 and 2011, at the National Cancer Center, Korea) to evaluate the association between ABO blood group, hepatitis B virus (HBV) and hepatitis C

virus (HCV) infection the development of pancreatic cancer suggested that the non-O blood types and anti-HCV seropositivity, but not HBV infection, may increase the risk of developing pancreatic cancer in Korea, where HBV is endemic⁽³⁸⁾. Patients with blood group O had a lower incidence of pancreatic cancer, compared to those with non-O blood groups, consistent with previous reports.

One study investigated the relationship of pancreatic cancer incidence with ABO blood group in Western Pennsylvania regional population. The ABO blood group frequency was compared between patients, individual, community-based blood donors between 1979 and 2009, showing the frequency of blood group A was statistically significantly higher amongst pancreatic cancer patients compared to its frequency amongst the regional blood donors showed conversely, the frequency of blood group O significantly lower amongst pancreatic cancer patients relative to the community blood donors and there were limited blood group B pancreatic cancer patients, concluded that the ABO blood group is associated with pancreatic cancer risk⁽¹⁷⁾.

The ABO blood group distribution in 119 in-patients with carcinoma of the pancreas, all patients had laparotomy with a macroscopic diagnosis of the tumour, or a post-mortem examination with histological confirmation of the diagnosis, showed a deficiency of blood group A and an excess of blood group B when compared with the controls⁽²⁸⁾.

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⁽²⁾. However, the nature of this association and the influence of specific ABO genotypes on the risk of pancreatic cancer remain unknown.

Evidence in the form of publications in medical and scientific literature dealing with the association of a certain ABO blood type with a certain malignancy is aplenty⁽¹⁵⁾. Studies before 1950 are not very reliable because of the lack of selection of the large numbers needed for a study to be really informative, the inadequate controls used, and the lack of awareness of the wide variations of ABO frequencies occurring over relatively limited areas even in populations considered ethnically homogeneous⁽¹³⁾.

Further studies are now needed to investigate the mechanisms by which the association between ABO blood group antigens and variants in other loci, such as the hTERT locus, contribute to pancreatic cancer susceptibility. GWASs are very useful for identifying common low-penetrance alleles that contribute to disease susceptibility^(16,19,20), and diseases that have gone through several rounds of GWASs and post-GWAS validation continue to yield important new findings and to refine the significance of earlier findings⁽²²⁾. Understanding the genetic and biological mechanisms of pancreatic cancer will eventually improve our ability to diagnose and treat this deadly disease⁽²⁶⁾.

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