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BRIEF ARTICLE

Significant association between ABO blood group and pancreatic cancer

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Abstract

AIM: To evaluate whether the ABO blood group is related to pancreatic cancer risk in the general population of the United States.

METHODS: Using the University of Pittsburgh's clinical pancreatic cancer registry, the blood donor database from our local blood bank (Central Blood Bank), and the blood product recipient database from the regional transfusion service (Centralized Transfusion Service) in Pittsburgh, Pennsylvania, we identified 274 pancreatic cancer patients with previously determined serological ABO blood group information. The ABO blood group frequency was compared between these patients and 708 842 individual, community-based blood donors who had made donations to Pittsburgh's Central Blood Bank between 1979 and 2009.

RESULTS: The frequency of blood group A was statistically significantly higher amongst pancreatic cancer patients compared to its frequency amongst the regional blood donors [47.63% *vs* 39.10%, odds ratio (OR) = 1.43, P = 0.004]. Conversely, the frequency of blood group O was significantly lower amongst pancreatic cancer patients relative to the community blood donors (32.12% *vs* 43.99%, OR = 0.60, P = 0.00007). There were limited blood group B (n = 38) and AB (n = 17) pancreatic cancer patients; the overall P trend value comparing patient to donor blood groups was 0.001.

CONCLUSION: The ABO blood group is associated with pancreatic cancer risk. Future studies should examine the mechanism linking pancreatic cancer risk to ABO blood group.

Key words: ABO blood group; Pancreatic adenocarcinoma; Surveillance; Risk reduction; Epidemiology

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INTRODUCTION

Pancreatic adenocarcinoma is the fourth most common cancer in the United States among men and women and has the highest case-fatality rate of any of the major cancers, due to its late stage at diagnosis and poor response to traditional therapies[1]. The median survival of pancreatic cancer patients is about 6 mo, and the majority of patients do not have resectable disease at the time of their diagnosis[2]. Pancreatic cancer increases in likelihood with advancing age and predominates in certain ethnic/racial groups, such as African-Americans, Ashkenazi Jews, Pacific Islanders, and the New Zealand Maori[3]. The elevated risk among certain populations appears to be multifactorial in nature and likely is due to a combination of environmental and inherited factors. The most significant genetic variables that are associated with the development of pancreatic cancer remain to be identified, although various cancer syndromes and hereditary pancreatitis place individuals at significantly increased risk[4]. Cigarette smoking, chronic pancreatitis, diabetes mellitus and obesity are well-established risk factors for pancreatic cancer[5].

Mounting evidence has demonstrated that the ABO blood group may also be associated with pancreatic cancer. A Spanish study of 108 cases and 374 controls found a non-significantly elevated risk of pancreatic cancer among individuals with blood group A [relative risk (RR) = 1.52, 95% confidence interval (CI): 0.87-2.67][6]. An Italian series of 224 patients with histologically-confirmed pancreatic adenocarcinoma compared the ABO blood group distribution with two control groups: 7086 patients with various diseases (Group 1) and 7320 voluntary blood donors (Group 2). The researchers noted an increased incidence of pancreatic cancer among the blood group B patients (RR = 1.5 *vs* Group 1, $P = 0.021$; RR = 1.7 *vs* Group 2, $P = 0.0025$) and a decreased number in blood group O patients, when compared with the two control groups[7]. Additionally, a combined, prospective cohort study of over 107 000 US health professionals observed that blood groups A, B, and AB were associated with an overall increased risk of developing pancreatic cancer[8]. More recently, a genome-wide association study (GWAS) of 1896 individuals with pancreatic cancer and 1939 controls - validated using an additional 2457 affected individuals and 2654 controls - identified a single nucleotide polymorphism (SNP) in intron 1 of the *ABO* gene (rs505922) as a genetic risk factor for pancreatic cancer [odds ratio (OR) = 1.20; 95% CI: 1.12-1.28][9]. In an effort to further discern how pancreatic cancer and the ABO blood group might be associated, we investigated the relationship of pancreatic cancer incidence with ABO blood group in our Western Pennsylvania regional population. We 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.

MATERIALS AND METHODS

To estimate the ABO frequencies in our local area, the donor database of the Central Blood Bank in Pittsburgh, Pennsylvania was queried for the ABO group of individual donors. The Central Blood Bank collects blood mainly in southwestern Pennsylvania. This database includes all individuals who have made a blood donation to the Central Blood Bank over the past approximately 30 years. Between 1979 and 2009, there were 708 842 unique blood donors. Pancreatic cancer patients from the University of Pittsburgh's affiliated hospitals - Presbyterian University Hospital and the University of Pittsburgh Cancer Institute's Hillman Cancer Center - who had provided informed consent to be part of their pancreatic cancer research registry were included in this study. Of 359 eligible pancreatic cancer patients in the registry, 274 had a historical or current ABO blood group available after querying the Centralized Transfusion Service's database. The Centralized Transfusion Service's database includes all patients who have a type and screen performed at Pittsburgh area hospitals. Blood donors were screened for infectious diseases according to Food and Drug Administration (FDA) and American Association of Blood Banks (AABB) regulations. FDA approved manual and automated ABO grouping methods and reagents were employed both at the Central Blood Bank and at the Centralized Transfusion Service. Proportions of ABO blood groups for pancreatic cancer cases and regional blood donors were compared using Chi-squared analysis. Data analysis was performed using R Project software (www.r-project.org).

RESULTS

Table 1 shows the OR of the ABO blood group distribution of the 274 pancreatic cancer patients in comparison with the ABO groups of the 708 842 unique blood donors to the Central Blood Bank in the Pittsburgh area over approximately the past 30 years. The frequency of blood group A was statistically significantly higher amongst the pancreatic cancer patients compared to the frequency amongst the regional blood donors. Conversely, the frequency of blood group O was statistically significantly lower amongst the pancreatic cancer patients relative to the community blood donors.

Statistically significant associations were not revealed among the limited number of blood group B ($n = 38$) and AB ($n = 17$) pancreatic cancer patients and regional blood donors; the overall P trend value comparing patient to donor ABO blood groups was 0.001.

DISCUSSION

Our study demonstrates that pancreatic cancer patients

Table 1 Odds ratio of pancreatic cancer patients stratified by ABO group in relation to the ABO groups of regional unique blood donors

Blood group	Unique blood donors, *n* (%)	Pancreatic cancer patients, *n* (%)	Odds ratio *vs* other blood groups
Group A	277 133 (39.10)	131 (47.63)	1.43 (0.004)
Group B	87 252 (12.31)	38 (13.87)	1.15 (0.41)
Group AB	32 662 (4.61)	17 (6.20)	1.37 (0.19)
Group O	311 795 (43.99)	88 (32.12)	0.60 (0.000070)
Total	708 842	274	*P* trend patients *vs* donors = 0.001

treated at a large, US institution are significantly more likely to be blood group A than regional blood donors and are significantly less likely to be blood group O than regional blood donors; the proportions of patient *vs* donor ABO blood groups were statistically different from what would be expected by chance alone. We examined this relationship among over 700 000 unique individuals who made blood donations to the Central Blood Bank in Pittsburgh between 1979 and 2009. Although there was a trend for risk of pancreatic adenocarcinoma in association with blood groups B and AB, a statistically significant effect was not observed, likely due to limited study power for detecting differences in these small subpopulations of individuals.

In a prospective cohort study published in 2009 of 107 503 US residents derived from the Nurses' Health Study (77 360 eligible female nurses) and the Health Professionals Follow-up Study (30 143 eligible male health professionals), individuals with blood group A, B and AB were noted overall to have an elevated risk of pancreatic cancer compared to those participants with blood group O[8]. However, taking each study separately, only blood group B was associated with increased cancer risk. Notably, blood group was self-reported in that prospective study, although a validation analysis displayed a greater than 90% concordance rate between reported and actual ABO blood group. In our study, the presence of serologically-determined blood group information from the blood bank was an entry criterion; thus, there was no possibility of recall bias influencing our results.

The *ABO* locus is located on chromosome 9 and there are three main alleles in the system: *A101*, *B101*, and *O01*[10]. The *A101* allele encodes a glycosyltransferase that adds a terminal α-N-acetylgalactosamine to H antigen, producing the A antigen. Similarly the *B101* allele encodes a glycosyltransferase that adds a terminal α-D-galactose to H antigen, thus creating the B antigen. The most common types of *O* alleles contain a critical 1-bp deletion compared to the consensus *A101* allele and, if translated, would give rise to non-functional enzymes[10,11]. In a group O individual, the H antigen is not modified. In addition to studies of pancreatic cancer, numerous past studies have shown that blood group A is related to gastric cancer[12,13]. The precise biological reasons as to why there is a relationship between ABO blood group and certain cancers are unknown, although two recent GWAS demonstrated that particular SNPs at the *ABO* locus were associated with the inflammatory cytokines tumor necrosis factor[14] and intercellular adhesion molecule 1[15]. The ABO blood group has also been shown to be related to other biological processes; for example, although a definitive mechanism has not yet been elucidated, levels of von Willebrand factor (vWF) antigen have been statistically shown to correlate to the ABO group with group AB individuals demonstrating the highest average vWF levels and group O individuals having the lowest average vWF levels[16].

The ABO blood group is genetically-determined and therefore is not a modifiable risk factor as are cigarette smoking, body mass index, diet or other lifestyle-related variables. The risk of pancreatic cancer for individuals with blood group A has been replicated in several studies. Nonetheless, the magnitude of risk is not high enough to warrant clinical screening, especially considering that these approaches are still in the developing stages[17]. However, the risk of pancreatic cancer in individuals with blood group A (and likely B or AB) is nearly as strong as the risk of developing pancreatic cancer as a consequence of cigarette smoking; thus, the combination of multiple moderate risk factors (such as age and family history[18]) could be used to calculate whether some individuals are at high enough risk to warrant counseling for risk reduction strategies or inclusion in pancreatic cancer screening trials.

The importance of the ABO blood group in assessing pancreatic cancer risk is also highlighted by the lack of other global genetic risk factors identified in the GWAS by Amundadottir *et al*[9]. This study indicates that the etiology of pancreatic cancer is more complex than previously believed and likely represents an array of deleterious pathways. Although the mechanisms of pancreatic cancer oncogenesis have not been fully deciphered, the association of ABO blood group with pancreatic cancer risk has been confirmed.

COMMENTS

Background

Pancreatic adenocarcinoma has the highest case-fatality rate of any of the major cancers. Because there are no accepted population-based screening methods, identifying individuals at greatest risk of developing this lethal form of cancer is paramount to developing risk reduction strategies. Previous evidence has indicated that ABO blood group may influence the risk of developing pancreatic cancer.

Research frontiers

Blood groups A, B, and/or AB have been associated with pancreatic cancer in a limited number of past studies. Genome-wide association studies have also identified a risk locus in the *ABO* gene.

Innovations and breakthroughs

This study compared the frequency of ABO blood groups in a cohort of pancreatic cancer patients to the blood group distributions in greater than 700 000 community-based blood donors. The authors demonstrated that blood group A was statistically significantly higher and blood group O was significantly less frequent among pancreatic cancer patients than in community blood donors. In contrast to many past studies, the authors used serologically-confirmed blood group information.

Applications

ABO blood group information is valuable in predicting who may be at risk of developing pancreatic adenocarcinoma and should be incorporated into risk stratification and surveillance studies.

Peer review

The authors report an interesting study about the connection of ABO blood group and the development of pancreatic cancer. The paper is written well and good to read, the data presented clearly and the whole paper of relevance.

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