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A comparison of the risk of pancreatic adenocarcinoma development between individuals with different ABO blood group phenotypes: a meta-analysis

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Abstract

Pancreatic adenocarcinoma aetiology is complex and incompletely understood, and with incidence and mortality rate increasing annually, discovery of associated risk factors is essential. One such risk factor is ABO blood group phenotype; however, conflicting study results make it unclear whether individuals with one ABO phenotype are more at risk than individuals with a different ABO phenotype. Therefore, a meta-analysis was performed comparing the risk of pancreatic cancer development between individuals with different ABO blood group phenotypes. Database searches were conducted using the search terms ABO blood group OR ABO blood type AND pancreatic cancer OR pancreatic adenocarcinoma OR pancreatic carcinoma, and a meta-analysis was then conducted on eligible studies. Twenty-one studies totalling 5,952,008 participants were analysed. The odds ratios (OR) for the comparison of pancreatic cancer development between individuals with different ABO phenotypes were determined; A vs. B (1.20, p=0.0002), AB (1.16, p=0.007), and O (1.38, p<0.00001); B vs. A (0.84, p=0.0002), AB (0.94, p=0.14), and O (1.16, p=0.0005); AB vs. A (0.86, p=0.007), B (1.06, p=0.14), and O (1.20, p=0.001); O vs. A (0.72, p<0.00001), B (0.86, p=0.0005), and AB (0.83, p=0.001). Individuals with blood group A have a significantly increased risk of pancreatic cancer development compared to all other ABO phenotypes, whereas blood group O individuals are significantly less at risk compared to all other ABO phenotypes. These results could influence eligibility of individuals for future pancreatic cancer screening programmes; however, further research is required to determine the mechanism by which ABO phenotypes can promote tumorigenesis.

Keywords: Pancreatic adenocarcinoma, ABO blood group, ABO phenotypes, risk factors, cancer development

Introduction

In the UK, pancreatic cancer is the 10th most common cancer and is soon expected to become one of the top three leading causes of cancer mortality (Rawla *et al*., 2019). Globally, there were approximately 495,000 new cases of pancreatic cancer in 2020 and 466,000 deaths attributed to the malignancy in the same year (Sung et al., 2021). There are two main types of pancreatic cancer; the most common of which is pancreatic adenocarcinoma which accounts for approximately 90% of cases and originates in the pancreatic exocrine glands, and the second type is pancreatic neuroendocrine tumours which arise in the pancreatic endocrine tissue and make up less than 5% of cases (Hidalgo et al., 2015). The malignancy is classified into 4 stages based on the tumour's clinical features; stage 1 cancer is localised to the pancreas only, measuring up to 4cm in size; stage 2 is found in the pancreas or spread to local lymph nodes and is larger than 4cm; stage 3 may have spread to blood vessels or nerves nearby; stage 4 pancreatic cancer has spread to other tissues (De La Cruz et al., 2014). Pancreatic adenocarcinoma does not typically present symptoms during early stages; therefore, diagnosis usually occurs when symptoms have manifested at stage 3 or 4 by which time the tumour is unresectable, resulting in poor prognosis (Rawla *et al*., 2019) and a 5-year survival rate of just 3-7% (Wang *et al*., 2020). With incidence increasing annually, understanding the disease pathogenesis and managing associated risk factors is essential. Pancreatic cancer has a complex aetiology that is not fully understood; however, smoking, obesity, type-2 diabetes, and chronic pancreatitis have been found to increase the risk of pancreatic cancer development (Mizrahi et al., 2020). Additionally, 5-10% of cases are expected to be due to specific genetic predispositions such as inheriting the BRCA2 mutation, having Lynch syndrome (Rawla et al., 2019), or potentially having a particular ABO blood group phenotype (hereafter referred to as ABO phenotype).

The ABO blood group is one of the main human blood group systems and classification is based on the expression of A and B antigens (Daniels, 2008). These antigens are oligosaccharides bound to lipids or proteins on the extracellular surface of red blood cell (RBC) membranes and determine whether an individual is blood group A, B, AB, or O (Rummel and Ellsworth, 2016). Located on chromosome 9q34.2, the *ABO* gene has three alleles, A, B, and O, that encode A and B glycosyltransferases and an inactive glycosyltransferase, respectively. The A and B alleles differ by seven nucleotide substitutions, and so the glycosyltransferase enzymes encoded have different specificities, facilitating the production of different antigens, A and B (Storry and Olsson, 2009), as seen in figure 1. As the expression of ABO alleles is codominant (Calafell *et al*., 2008), inheritance of one copy of each allele results in the production of both glycosyltransferases and subsequently, both antigens, creating the AB phenotype (Franchini *et al*., 2016). However, the O variant of the *ABO* gene has a single base deletion at position 261 causing a frameshift that results in a premature stop codon (Rummel and Ellsworth, 2016). This subsequently results in the production of a truncated, non-functioning glycosyltransferase which is unable to modify the precursor H antigen. Inheritance of two copies of the O allele results in a complete lack of glycosyltransferase activity and hence lack of A or B antigen production, giving rise to blood type O (Franchini *et al*., 2016). Along with the existence of A and B antigens on RBC membranes, ABO phenotypes are also associated with serum antibodies that occur naturally against the antigen that is not present on the RBC surface, for example blood group B individuals have anti-A

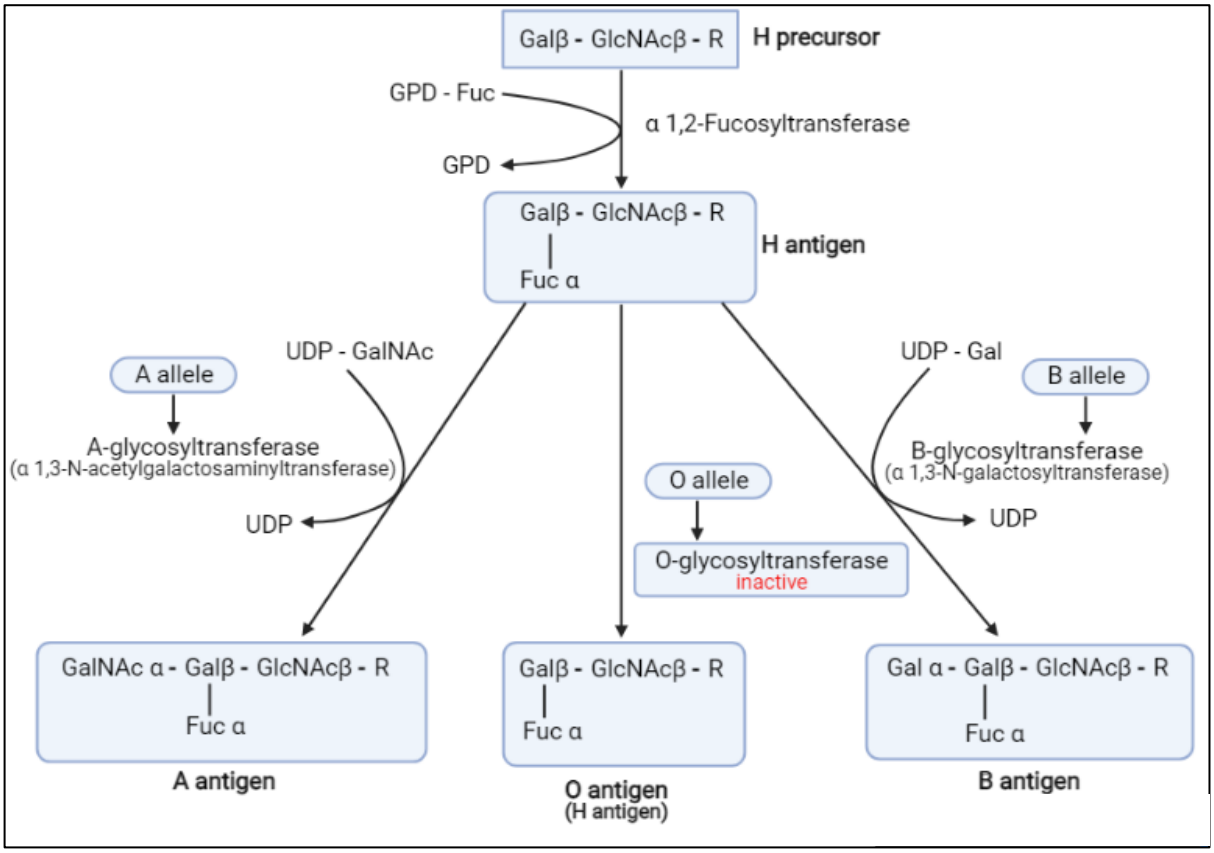

Figure 1: The biosynthetic pathways for the formation of the ABO blood group antigens. The H antigen is formed by the attachment of a fucose group to the terminal galactose residue of a H precursor molecule by a α1,2-fucosyltransferase. The H antigen then serves as a precursor for the production of the ABO blood group antigens. The A allele encodes the A-glycosyltransferase which catalyses the attachment of N-acetylgalactosamine to the galactose residue on the H antigen, forming the A antigen. Similarly, the B antigen encodes the B-glycosyltransferase which catalyses the attachment of D-galactose to the galactose residue of the H antigen, producing the B antigen. The O allele encodes an inactive glycosyltransferase enzyme that is unable to alter the H antigen, leaving it with a single fructose moiety as the terminal residue (Storry and Olsson, 2009; Franchini et al., 2016). R represents the core structure of the H precursor. Fuc: fucose, Gal: D-galactose, GalNAc: N-acetylgalactosamine, GlcNAc: N-acetylglucosamine (Image created using BioRender; adapted from Watkins, 2001 and Hosoi, 2008)

antibodies and blood group O individuals have anti-A and anti-B antibodies (Calafell *et al*., 2008). After the discovery of the 4 basic ABO phenotypes, it was found that some blood group A RBCs reacted differently to an antibody named anti-A_1, and so blood group A was split into A_1 and A_2 phenotypes; both react with anti-A, but only A_1 phenotypes also react with anti-A_1 (Storry and Olsson, 2009). In addition to the surface of erythrocytes, ABO antigens are expressed in bodily fluids and on several other human cell and tissue types, including platelets, vascular endothelium, and epithelium; therefore, extending the clinical importance of this blood group system further than its previous haematological and transfusion medicine boundaries (Franchini and Lippi, 2015).

The ABO blood group has been associated with the development of many diseases including cardiovascular diseases such as coronary heart disease and thromboembolisms (Franchini and Lippi, 2015), infectious diseases such as malaria

and cholera (Anstee, 2010), and cancer, including pancreatic cancer. Since 1960, studies have established a significant link between the ABO blood group and pancreatic cancer development, leading to a plethora of investigations studying the risk of cancer development between individuals with different ABO phenotypes. However, due to conflicting results, it remains unclear whether individuals with one ABO phenotype are more at risk of pancreatic cancer development compared to individuals with a different ABO phenotype. For example, a study by Wolpin *et al.* (2009) found that participants with blood type B had the highest risk of pancreatic cancer development compared to those with blood group O, whereas Engin *et al.* (2012) found that individuals with blood group A had a significantly higher risk of pancreatic cancer and blood group AB individuals had a significantly lower risk. The first and only meta-analysis examining ABO phenotypes and risk of pancreatic cancer was published in 2013 and summarised data collected between 2006 and 2011 (Risch *et al*., 2013), so it was beneficial to update this analysis and integrate data collected from recently published studies. Surgery provides the best treatment for pancreatic cancer and drastically increases survival rate; however, this option is only available for patients with non-invasive cancer (Rizzato *et al*., 2013), therefore, identification and diagnosis in the early stages or precursive intraepithelial neoplastic stage is essential. Uncovering genetic risk factors, such as ABO phenotype, will potentially provide selection criteria for identifying at-risk individuals that may benefit from the establishment of pancreatic screening programmes, leading to early diagnosis, reduced mortality, and increased survival rate of this disease (Lennon *et al*., 2010).

The aim of this meta-analysis was to compare the risk of pancreatic cancer development between individuals with different ABO blood group phenotypes to establish whether individuals with one ABO phenotype are more at risk of pancreatic cancer development than individuals with a different ABO phenotype.

Methodology

Search strategy

Systematic searches of the literature were performed using PubMed, Primo, and Web of Science databases for studies investigating an association between ABO phenotypes and pancreatic cancer development. In addition, the reference lists of relevant reviews, meta-analyses and studies were searched to identify further studies for inclusion. The search strategy included the search terms “ABO blood group” OR “ABO blood type” AND “pancreatic cancer” OR “pancreatic adenocarcinoma” OR “pancreatic carcinoma”. Multiple combinations of these search terms, listed in table 1, were used in each database to ensure that all relevant studies were retrieved and to reduce search bias. Searches of the literature were conducted up until 15th January 2021.

Table 1: Combinations of the search terms used in PubMed, Primo, and Web of Science databases to identify and retrieve all relevant studies for potential inclusion in the meta-analysis.

Combination of search terms used
“ABO blood group” and “pancreatic cancer”
“ABO blood group” and “pancreatic adenocarcinoma”
“ABO blood group” and “pancreatic carcinoma”
“ABO blood type” and “pancreatic cancer”
“ABO blood type” and “pancreatic adenocarcinoma”
“ABO blood type” and “pancreatic carcinoma”
“ABO blood group” or “ABO blood type” and “pancreatic cancer”
“ABO blood type” or “ABO blood group” and “pancreatic adenocarcinoma”
“ABO blood type” or “ABO blood group” and “pancreatic carcinoma”
“ABO blood type” or “ABO blood group” and “pancreatic cancer” or “pancreatic adenocarcinoma”
“ABO blood type” or “ABO blood group” and “pancreatic cancer” or “pancreatic carcinoma”
“ABO blood type” or “ABO blood group” and “pancreatic carcinoma” or “pancreatic adenocarcinoma”
“ABO blood group” and “pancreatic cancer” or “pancreatic adenocarcinoma”
“ABO blood group” and “pancreatic cancer” or “pancreatic carcinoma”
“ABO blood group” and “pancreatic carcinoma” or “pancreatic adenocarcinoma”
“ABO blood type” and “pancreatic cancer” or “pancreatic adenocarcinoma”
“ABO blood type” and “pancreatic carcinoma” or “pancreatic adenocarcinoma”
“ABO blood type” and “pancreatic cancer” or “pancreatic carcinoma”
“ABO blood group” and “pancreatic cancer” or “pancreatic adenocarcinoma” or “pancreatic carcinoma”
“ABO blood type” and “pancreatic cancer” or “pancreatic adenocarcinoma” or “pancreatic carcinoma”
“ABO blood group” or ABO blood type” and “pancreatic cancer” or “pancreatic carcinoma” or “pancreatic adenocarcinoma”

Selection criteria

Eligibility of the literature was assessed, and articles were included if: (1) the study was a case-control or cohort study; (2) frequencies of each ABO phenotype were reported for participants with and without pancreatic cancer; and (3) the study reported more than 100 pancreatic cancer cases. Studies were considered regardless of publication language, publication date, and publication country to reduce search bias. Studies published in non-English languages (n=1) were translated using Google translate. Review papers and meta-analyses were excluded. Studies that did not have the desired outcome measure or lacked a healthy control group (in the instance of case-control studies) were excluded. Studies that investigated the development of cancers other than pancreatic adenocarcinoma (including pancreatic neuroendocrine tumours), or the development of benign pancreatic conditions (e.g., pancreatitis), or investigated associations with blood groups other than ABO, were all excluded. Studies that presented data as percentages or odds ratios rather than exact numbers were considered to have insufficient data and were excluded, as were studies that did not include the number of participants with each ABO phenotype separately. If data was published in more

than one study, only the study providing the most information was included. Access to full articles was limited in some cases which restricted the number of studies that could be assessed for inclusion in the meta-analysis.

Data extraction
From the selected studies, information was extracted, including basic information of the studies, such as authors, publication year, and study design; characteristics of the study population, including country in which the study was conducted, and the source of the control group (in case-control studies); and the outcome measure which was the number of participants with and without pancreatic cancer in each study.

Participants
This meta-analysis analysed case-control and cohort studies that had reported the incidence of pancreatic adenocarcinoma in participants who were either blood type A, B, AB, or O.

Intervention(s), exposure(s)
This meta-analysis considered the ABO blood group phenotype of each participant to be the exposure.

Comparator(s) and control group
This analysis compared the incidence of pancreatic cancer in participants with one ABO phenotype with the incidence of pancreatic cancer in participants with each of the other three ABO phenotypes. Four analyses were conducted where each ABO phenotype was used as the main comparator group sequentially for comparison against each of the other ABO phenotypes that were added as subgroups. For more detail, refer to the statistical analysis section.

Outcome(s)
The outcome analysed in this meta-analysis was the incidence of pancreatic adenocarcinoma for each ABO phenotype.

Statistical analysis
Odds ratios (ORs) were calculated for the dichotomous data for A vs. B, AB, and O, B vs. A, AB, and O, AB vs. A, B, and O, and O vs. A, B, and AB based on the number of participants that had pancreatic cancer and the number that did not have pancreatic cancer with each ABO phenotype. Subgroup analyses were conducted to compare the incidence of pancreatic cancer between individuals with one ABO phenotype and individuals with each of the other three ABO phenotypes. Four separate analyses were conducted; a different ABO phenotype (A, B, AB, or O) was used as the main comparator group in each analysis with the other three ABO phenotypes added as subgroups. In each of the analyses, the outcome of the main comparator ABO phenotype was compared to the outcome of each of the subgroup ABO phenotypes sequentially to calculate respective ORs. An odds ratio is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Forest plots were produced to assess the ORs and 95% confidence intervals across studies, and p values <0.05 were considered significant. Heterogeneity of ORs between studies was evaluated by the I^2 statistic, where a value of 0% suggests no evidence of heterogeneity, 50% was considered moderate heterogeneity, and a value of 100% indicates considerable heterogeneity between studies. Publication bias was

evaluated on visual inspection of funnel plots where presence of bias would result in a non-symmetrical graph. All analyses were performed using RevMan 5.4.1 (Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects inverse variance model was used throughout the analysis.

Results

Literature search

Using the search strategy, 3,450 articles were retrieved. After screening the title and abstracts, 3,412 were excluded as they were either irrelevant, a review article, or a duplicated study, and 38 remained for full-text review. Following this, 19 were excluded for reasons listed in table 2, and 2 additional studies were identified in the reference lists of candidate articles and fulfilled the inclusion criteria. In total, 21 studies met the inclusion criteria and were included in the meta-analysis. The process of study selection is demonstrated in figure 2.

Table 2: Studies excluded from the meta-analysis following full text assessment due to not meeting the inclusion criteria of being a case-control or cohort study, reporting the frequencies of each ABO phenotype for participants both with and without pancreatic cancer, and reporting more than 100 pancreatic cancer cases. The reason(s) for exclusion of each study are listed.

Study	Reason for exclusion
Amundadottir *et al*., 2009	Analyses data from an already included study
Antwi *et al*., 2018	Analyses data from an already included study
Gong *et al*., 2012	Data expressed as percentages and inappropriate control group using individuals diagnosed with other types of cancer
Hsiao *et al*., 2015	Less than 100 cancer cases
Iodice *et al*., 2010	No data for control group without pancreatic cancer
Kos *et al*., 2012	No healthy control group without pancreatic cancer
Lennon *et al*., 2010	Review article
Li *et al*., 2015	No healthy control group without pancreatic cancer
Li *et al*., 2020	No healthy control group without pancreatic cancer
MacAfee 1964	Data for blood groups B and AB were combined
Pelzer *et al*., 2013	Data expressed as percentages
Risch *et al*., 2010	A, B and AB data were combined as non-O
Risch *et al*., 2015	A, B and AB data were combined as non-O
Tanaka *et al*., 2020	No healthy control group without pancreatic cancer
Vasan *et al*., 2016	No data for blood group O
Wang *et al*., 2012b	No healthy control group without pancreatic cancer and no data for the number of pancreatic cancer cases with each blood group phenotype separately
Wolpin *et al*., 2010b	Analyses data from an already included study
Xu *et al*., 2014	No raw data for number of people with each blood group phenotype
Zhang *et al*., 2014	Meta-analysis and review

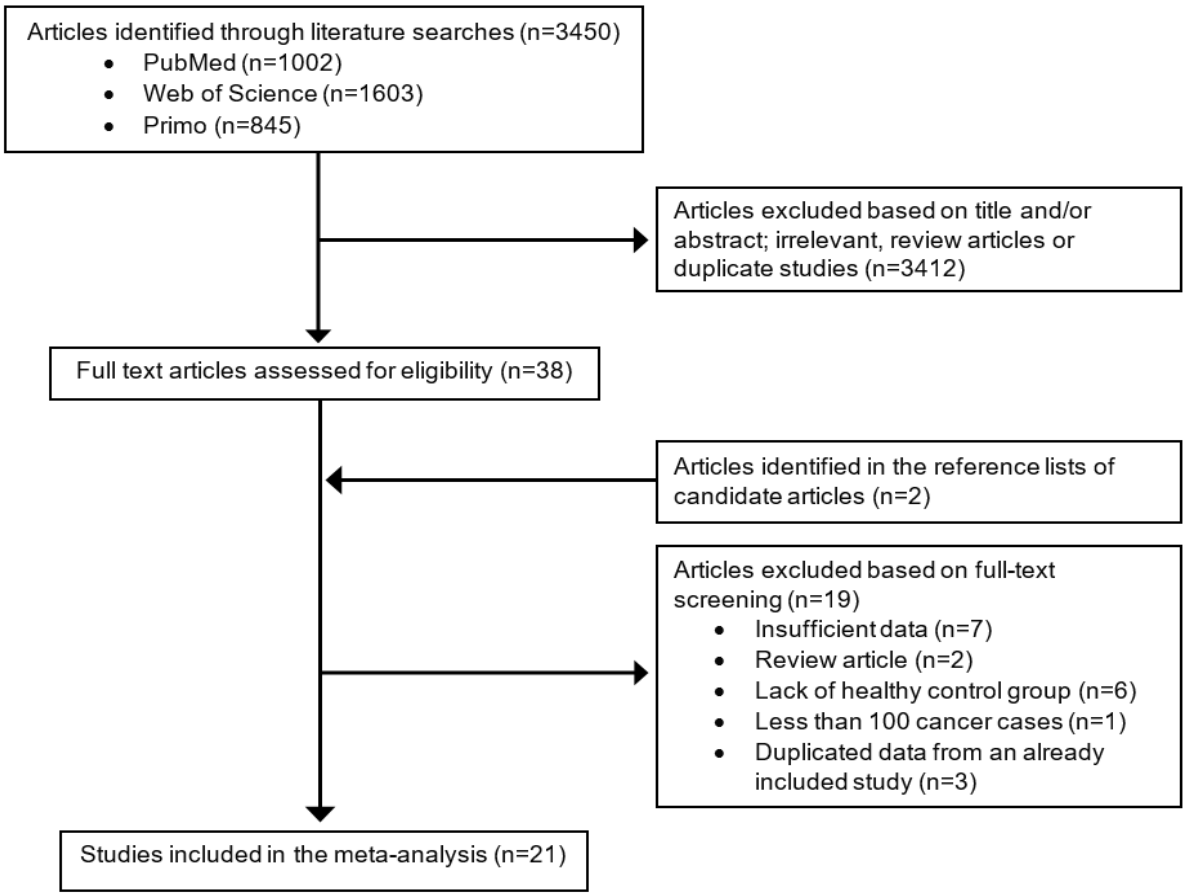

Figure 2*:* A consort figure demonstrating the process of study selection for inclusion in the meta-analysis. Each stage of the screening process is stated including reasons why articles were excluded at each stage and how many articles were left for inclusion in the meta-analysis (n represents the number of articles).

Study characteristics

The 21 studies included in the meta-analysis had a total of 5,952,008 participants, 15,924 of which had pancreatic adenocarcinoma. The characteristics of the included studies are summarised in table 3. These studies were conducted in 10 countries, published between 1960 and 2019. The source of the control groups in the case-control studies were mainly blood donors, hospital patients with no history of cancer, or randomly selected residents.

Blood groups and risk of pancreatic cancer

Of the 15,924 pancreatic cancer cases, 6,491 patients had blood type A (41%), 4,913 had blood type O (31%), 3,251 had blood type B (20%), and 1,269 patients had blood type AB (8%).

Blood group A

In total, 6,491 of 2,238,174 (0.29%) type A participants had pancreatic cancer compared with 9,433 of 3,713,834 (0.25%) of non-A participants.

Table 3: The characteristics of studies included in the meta-analysis comparing the risk of pancreatic cancer between individuals with different ABO blood group phenotypes

Study	Country	Study design	No. of pancreatic cancer cases	No. of controls	Source of control group (case-control studies only)
Aird *et al*., 1960	UK	Case-control	620	62,800	Blood donors
Ben *et al*., 2011	China	Case-control	1,431	1,449	Hospital patients with acute conditions
Egawa *et al*. 2013	Japan	Case-control	883	4,465,349	General Japanese population
El Jellas *et al*., 2017	Norway	Case-control	195	379	Blood donors
Engin *et al*., 2012	Turkey	Case-control	132	350	Blood donors
Greer *et al*., 2010	USA	Case-control	274	708,842	Blood donors
Huang *et al*., 2017	China	Prospective cohort	162	17,907	N/A
Klein *et al*., 2013	USA	Case-control	2,002	2,207	Randomly selected residents, friends and family of hospital patients, or hospital patients – all with no history of cancer
Li *et al*., 2018	China	Case-control	264	423	Hospital inpatients with non-malignant diseases
Liu *et al*., 2019	China	Case-control	3,063	200,660	Hospital patients without pancreatic cancer
Nakao *et al*., 2011	Japan	Case-control	185	1465	Non-cancer hospital outpatients
Newell *et al*., 1974	USA	Case-control	137	4995	Volunteers who donated blood to the hospital
Rahbari *et al*., 2012	Germany	Case-control	627	13,044	Hospital patients without pancreatic cancer
Risch *et al*., 2013	China	Case-control	846	971	Randomly selected Shanghai residents without malignant disease
Rizzato *et al*., 2013	Europe	Case-control	1,026	2,275	Blood donors and healthy volunteers
Sun *et al*., 2015	Taiwan	Prospective Cohort	156	339,276	N/A
Wang *et al*., 2012a	China	Case-control	627	711	Hospital patients with non-malignant diseases
Wolpin *et al*., 2009	USA	Prospective cohort	316	107,187	N/A
Wolpin *et al*., 2010a	USA	Case-control	1,534	1,583	Healthy matched controls based on age, gender, and ethnicity
Woo *et al*., 2013	Korea	Case-control	753	3,012	Healthy individuals in the Cancer Screening Cohort
Zhou and Li, 2005	China	Case-control	691	1,199	Hospital patients with non-tumour or endocrine disease

The ORs for the comparison of risk of pancreatic cancer development for blood group A vs. B, AB, and O are 1.20 (95% confidence interval [CI]: 1.09, 1.32; I^2 = 65%; p=0.0002), 1.16 (CI: 1.04, 1.30; I^2 = 45%; p=0.007), and 1.38 (CI: 1.31, 1.46; I^2 = 23%; p<0.00001) respectively (Figure 3). The odds of developing pancreatic cancer are significantly higher for blood group A individuals compared with the odds of individuals of all other blood group phenotypes.

Blood group B

In total, 3,251 of 1,257,448 (0.26%) type B participants had pancreatic cancer compared with 12,673 of 4,694,560 (0.27%) of non-B participants. The ORs for the comparison of risk of pancreatic cancer development for blood group B vs. A, AB, and O are 0.84 (CI: 0.76, 0.92; I^2 = 65%; p=0.0002), 0.94 (CI: 0.87, 1.02; I^2 = 3%; p=0.14), and 1.16 (CI: 1.07, 1.27; I^2 = 51%; p=0.0005) respectively (Figure 4). The odds of developing pancreatic cancer are significantly lower for individuals with blood group B compared with the odds of individuals with blood group A. However, the odds of developing pancreatic cancer are significantly higher for individuals with blood group B compared with the odds of individuals with blood group O. There are slightly reduced odds of blood group B individuals developing pancreatic cancer compared with the odds of individuals with blood group AB, but this is not significant (p=0.14).

Blood group AB

In total, 1,269 of 533,180 (0.24%) type AB participants had pancreatic cancer compared with 14,655 of 5,418,828 (0.27%) of non-AB participants. The ORs for the comparison of risk of pancreatic cancer development for blood group AB vs. A, B, and O are 0.86 (CI: 0.77, 0.96; I^2 = 45%; p=0.007), 1.06 (CI: 0.98, 1.15; I^2 = 3%; p=0.14), and 1.20 (CI: 1.07, 1.34; I^2 = 42%; p=0.001) respectively (Figure 5). The odds of developing pancreatic cancer are significantly lower for individuals with blood group AB compared with the odds of individuals with blood group A. However, the odds of developing pancreatic cancer are significantly higher for individuals with blood group AB compared with the odds of individuals with blood group O. There are slightly increased odds of blood group AB individuals developing pancreatic cancer compared with the odds of individuals with blood group B, but this is not significant (p=0.14).

Blood group O

In total, 4,913 of 1,923,206 (0.26%) type O participants had pancreatic cancer compared with 11,011 of 4,028,802 (0.27%) of non-O participants. The ORs for the comparison of risk of pancreatic cancer development for blood group O vs. A, B, and AB are 0.72 (CI: 0.69, 0.76; I^2 = 22%; p<0.00001), 0.86 (CI: 0.79, 0.94; I^2 = 51%; p=0.0005), and 0.83 (CI: 0.75, 0.93; I^2 = 42%; p=0.001) respectively (Figure 6). The odds of developing pancreatic cancer are significantly lower for individuals with blood group O compared with the odds of individuals of all other blood group phenotypes.

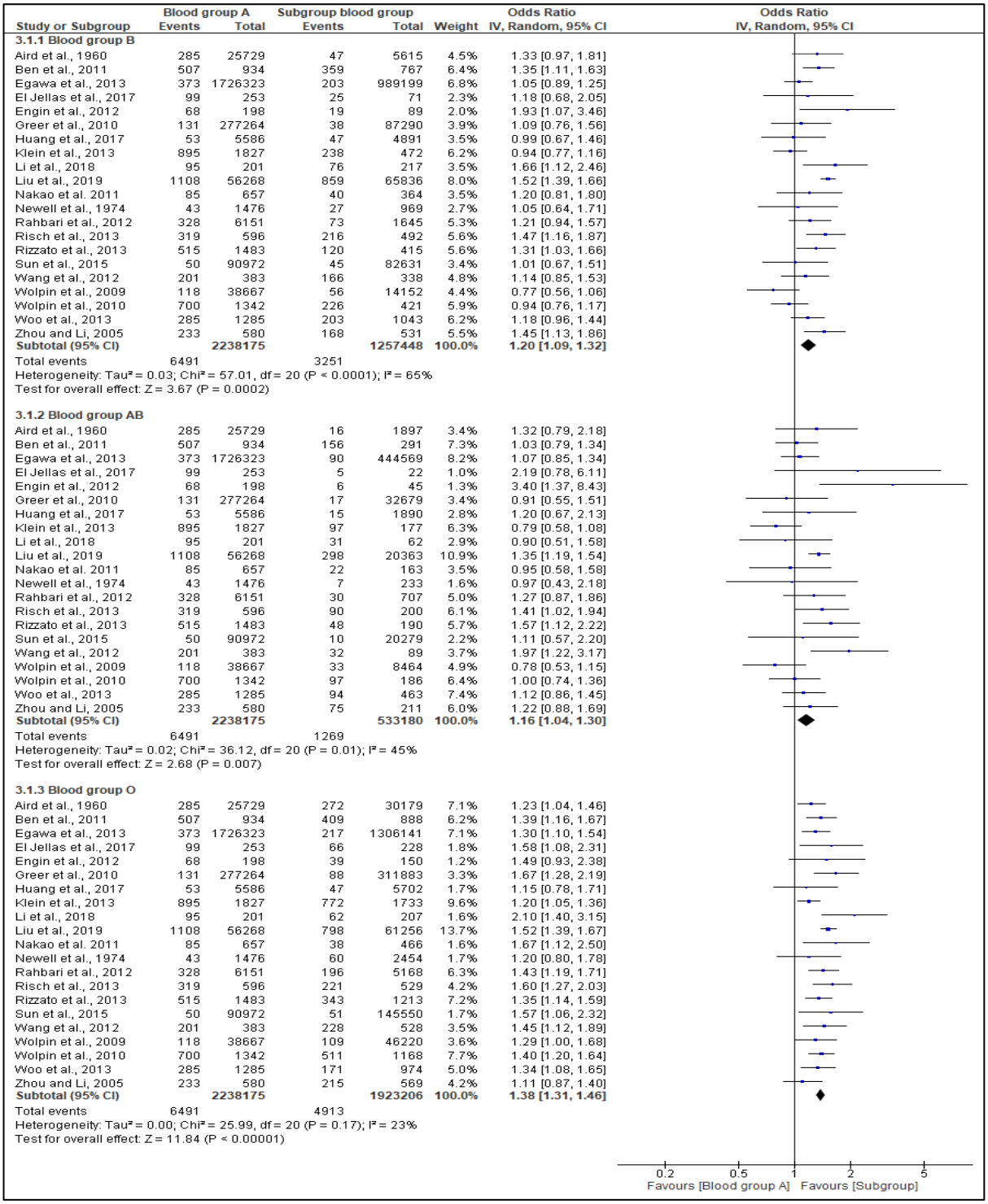

Figure 3: Forest plot showing the odds of developing pancreatic cancer between blood group A and each non-A blood group (B, AB, and O) that is listed separately as a subgroup. Events describe the number of participants that have pancreatic cancer with the given ABO blood group phenotype, and the total describes the total number of participants with the given ABO blood group phenotype (participants with pancreatic cancer and participants without pancreatic cancer). The tables summarize each study within each subgroup, and the graphs plot the odds ratio (OR) of each study within the subgroup (blue squares with black whiskers indicating 95% confidence intervals [CI], area of each square represents the relative weight of the study in the subgroup analysis) and the overall OR of each subgroup (the centre of the black diamond indicates the overall OR and the width of the diamond indicates the 95% CI)

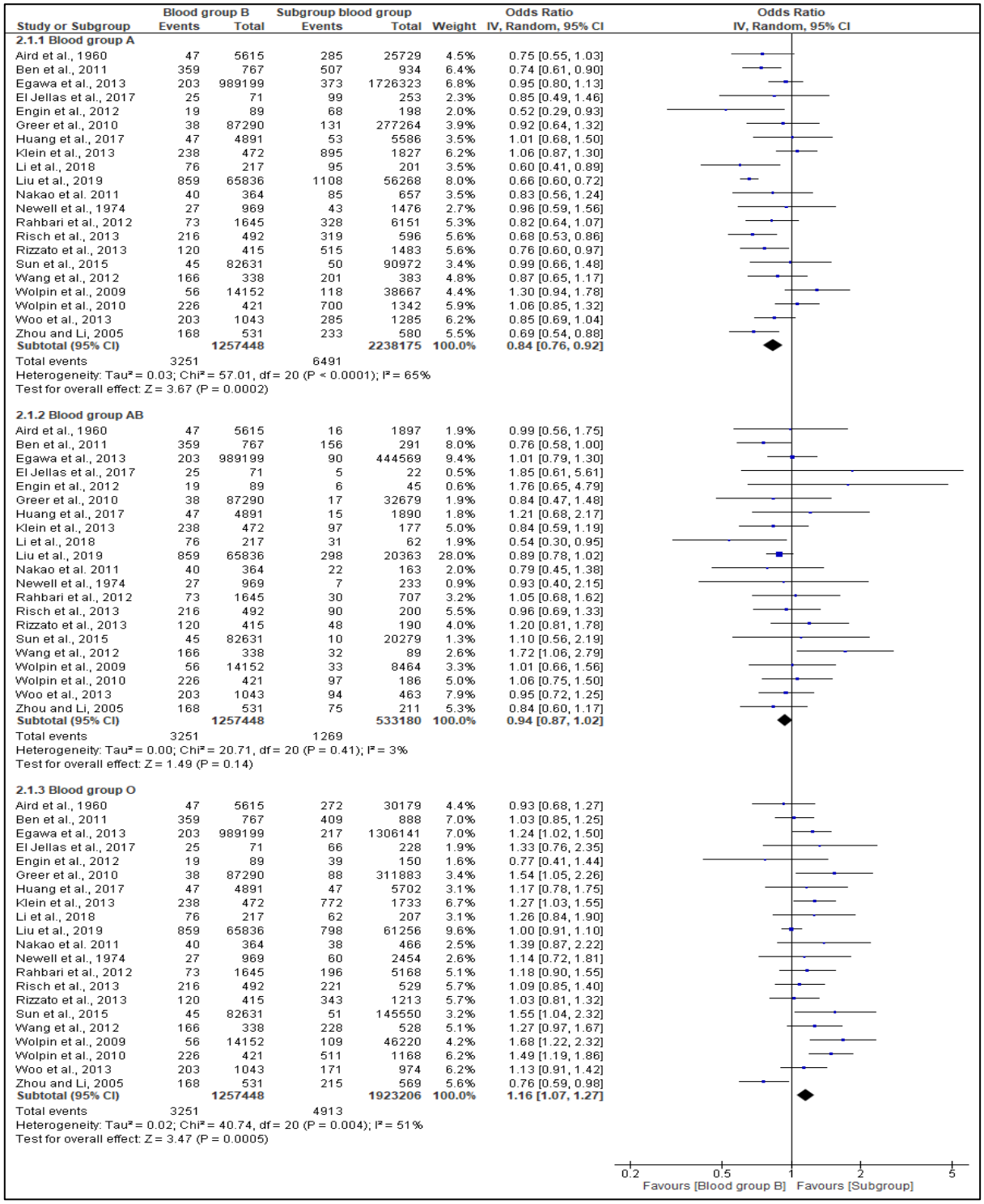

Figure 4: Forest plot showing the odds of developing pancreatic cancer between blood group B and each non-B blood group (A, AB, and O) that is listed separately as a subgroup. Events describe the number of participants that have pancreatic cancer with the given ABO blood group phenotype, and the total describes the total number of participants with the given ABO blood group phenotype (participants with pancreatic cancer and participants without pancreatic cancer). The tables summarize each study within each subgroup, and the graphs plot the odds ratio (OR) of each study within the subgroup (blue squares with black whiskers indicating 95% confidence intervals [CI], area of each square represents the relative weight of the study in the subgroup analysis) and the overall OR of each subgroup (the centre of the black diamond indicates the overall OR and the width of the diamond indicates the 95% CI)

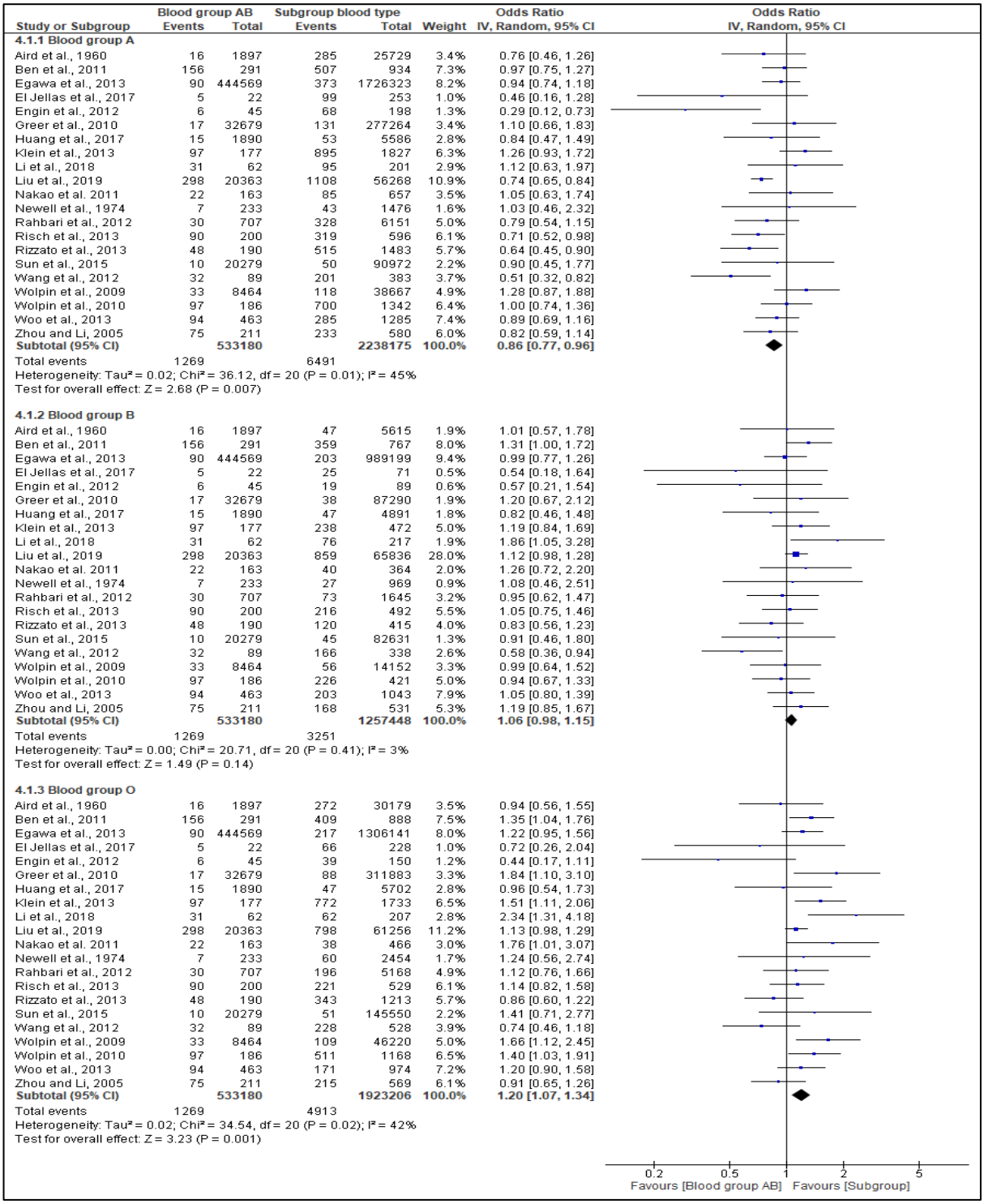

Figure 5: Forest plot showing the odds of developing pancreatic cancer between blood group AB and each non-AB blood group (A, B, and O) that is listed separately as a subgroup. Events describe the number of participants that have pancreatic cancer with the given ABO blood group phenotype, and the total describes the total number of participants with the given ABO blood group phenotype (participants with pancreatic cancer and participants without pancreatic cancer). The tables summarize each study within each subgroup, and the graphs plot the odds ratio (OR) of each study within the subgroup (blue squares with black whiskers indicating 95% confidence intervals [CI], area of each square represents the relative weight of the study in the subgroup analysis)) and the overall OR of each subgroup (the centre of the black diamond indicates the overall OR and the width of the diamond indicates the 95% CI)

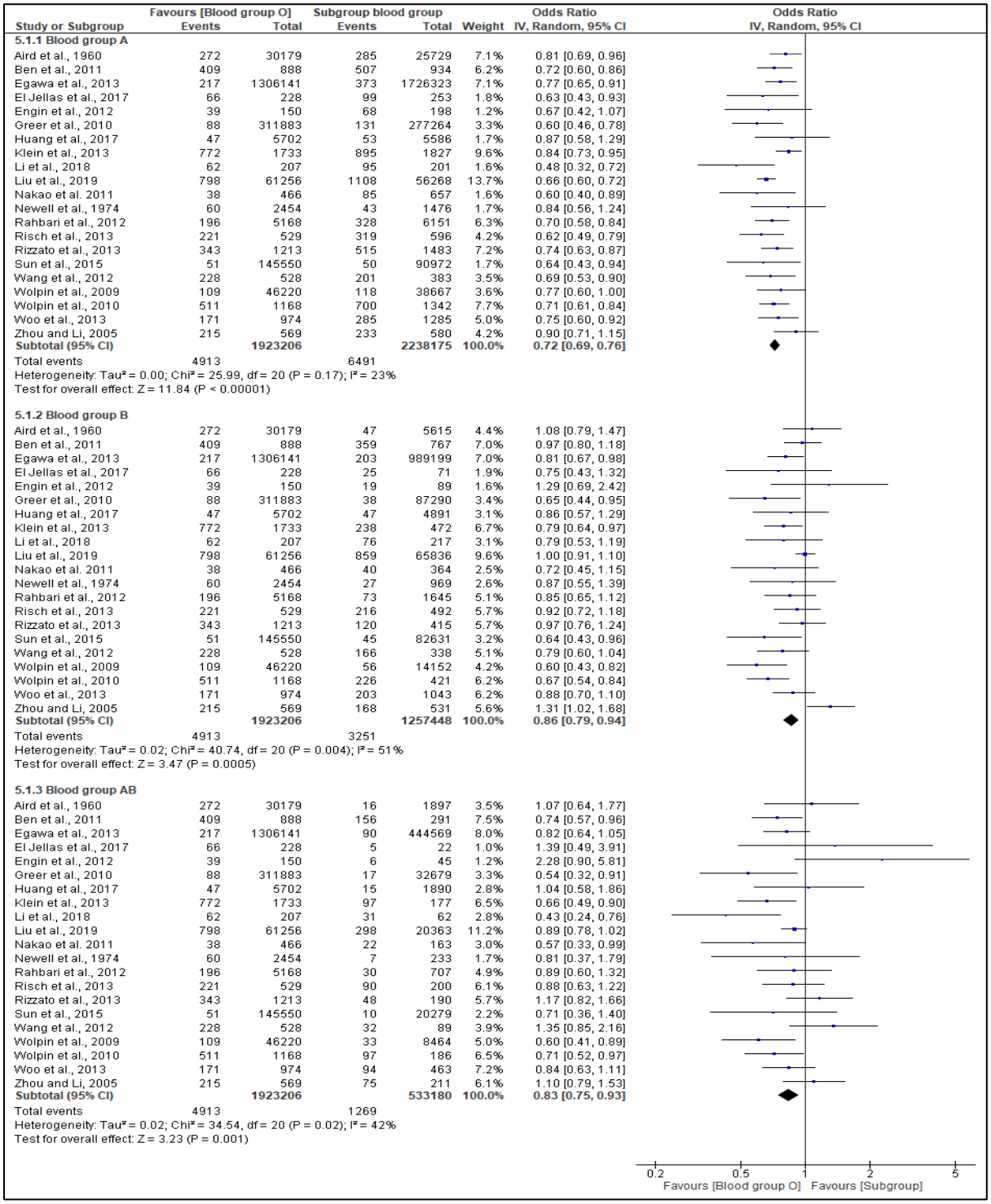

Figure 6: Forest plot showing the odds of developing pancreatic cancer between blood group O and each non-O blood group (A, B, and AB) that is listed separately as a subgroup. Events describe the number of participants that have pancreatic cancer with the given ABO blood group phenotype, and the total describes the total number of participants with the given ABO blood group phenotype (participants with pancreatic cancer and participants without pancreatic cancer). The tables summarize each study within each subgroup, and the graphs plot the odds ratio (OR) of each study within the subgroup (blue squares with black whiskers indicating 95% confidence intervals [CI], area of each square represents the relative weight of the study in the subgroup analysis)) and the overall OR of each subgroup (the centre of the black diamond indicates the overall OR and the width of the diamond indicates the 95% CI)

Analysis of publication bias

Funnel plots were produced to assess publication bias. No evidence of publication bias was present for A vs. B, AB, or O (Figure 7A), B vs. A, AB, or O (Figure 7B), AB vs. A, B, and O (Figure 7C), or O vs. A, B, or AB (Figure 7D); all plots were symmetrical.

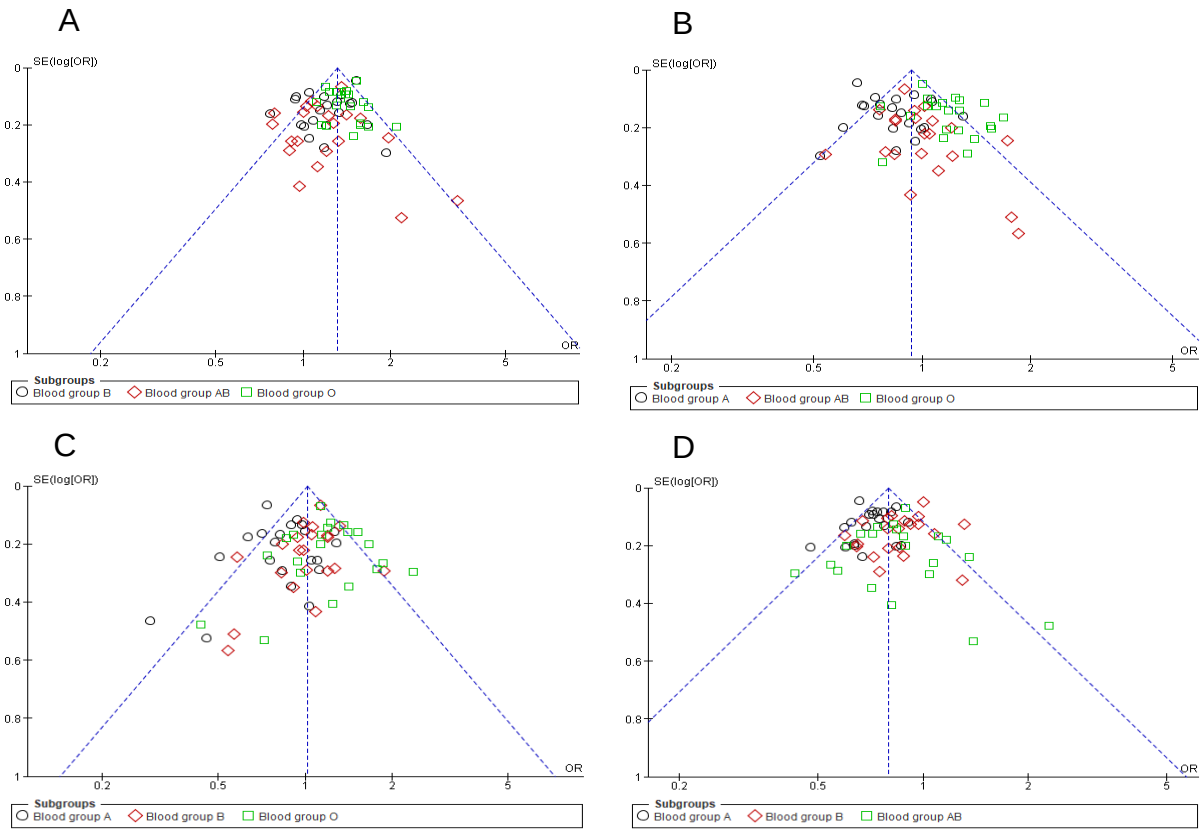

Figure 7: Funnel plots for comparisons of ABO blood group phenotype and risk of pancreatic cancer development. (A) blood group A vs. non-A phenotypes and risk of pancreatic cancer development, (B) blood group B vs. non-B phenotypes and risk of pancreatic cancer development, (C) blood group AB vs. non-AB phenotypes and risk of pancreatic cancer development, and (D) blood group O vs. non-O phenotypes and risk of pancreatic cancer development. Odds ratio (OR) is plotted for each study in each subgroup against the standard error of the OR. The centre blue dashed line represents the overall OR and the outer blue dashed lines represent the boundaries into which the studies would fall if there was no publication bias.

Discussion

In this meta-analysis, individuals with blood group A were found to have a significantly increased risk of developing pancreatic cancer compared to individuals with blood groups B ($p=0.0002$), AB ($p=0.007$), and O ($p<0.00001$), and individuals with blood group O had a significantly lower risk of developing pancreatic cancer compared to those with blood groups A ($p<0.00001$), B ($p=0.0005$), and AB ($p=0.001$), which is consistent with the results of many other studies, including the earlier meta-analysis conducted by Risch *et al*. (2013). There was no difference in the risk of developing pancreatic cancer between individuals with blood groups AB and B. However, although statistically insignificant ($p=0.14$), blood group AB did have a slightly increased risk compared to blood group B individuals. These results

suggest that individuals with blood group A are most at risk of pancreatic cancer development, followed by blood group AB and B, and blood group O individuals are least at risk. However, the mechanism by which the ABO blood group may cause or promote pancreatic cancer is unknown, although several plausible theories have emerged.

Following their investigation into the link between ABO blood group phenotypes and risk of pancreatic cancer development, Wolpin *et al*. (2010b) conducted a follow-up study using their data collected from the Pancreatic Cancer Cohort Consortium to investigate the effect of variant ABO blood group alleles, namely A_1 and A_2, on the risk of pancreatic cancer development. The A_1 allele produces the A_1-glycosyltransferase which is the main enzyme seen in blood group A individuals, however, the A_2-glycosyltransferase produced by the A_2 allele is present in a minority of blood group A individuals. The A_2-transferase was previously found to have a 30-fold reduction in enzymatic activity compared to A_1 transferase, leading to the production of fewer A antigens (Storry and Olsson, 2009). This reduction in activity may be attributed to the increased size of the A_2-glycosyltransferase in comparison to the A_1-transferase which is due to the deletion of a single cytosine residue at the coding region for the enzyme causing a frameshift which extends the open read frame and results in a protein structure with 21 additional amino acids (Svensson *et al*., 2009). Wolpin *et al*. (2010b) found that, compared to individuals with blood group O, inheritance of the A_2 allele and therefore production of A_2-glycosyltransferase did not increase the risk of developing pancreatic cancer, whereas inheritance of the A_1 allele did increase the risk of developing pancreatic cancer (Wolpin *et al*., 2010b). These results are supported by similar data obtained from the PANDoRA consortium which also suggested that the production of A_1-glycosyltransferase and not A_2-glycosyltransferase increases the risk of pancreatic cancer development compared to O glycosyltransferase (Rizzato *et al*., 2013). This could suggest that it is the reduced expression of the A antigen that decreases the risk of pancreatic cancer in individuals with the A_2 allele, and so the presence of the A antigen may be involved in tumorigenesis. This provides a possible explanation for the results seen in this meta-analysis as individuals with blood group A had a significantly increased risk of pancreatic cancer development compared to individuals of every other ABO phenotype, and additionally the presence of the A allele in individuals with blood group AB showed a non-significant increase in risk compared to blood groups B and O. However, this does not explain why individuals with blood group B were found to be more at risk of pancreatic cancer development compared to individuals with blood group O. It may be that the presence of either the A or B antigen increases an individual's risk of pancreatic cancer development, and so any individuals with blood group O that produce non-functioning enzymes and therefore no antigens, will have a significantly reduced risk compared to all other ABO phenotypes. With regards to the difference in risk seen between individuals with blood group A and those with blood group B, it may be that A_1-glycotransferase has a higher activity than B-glycosyltransferase which causes individuals with blood group A to have more antigens present on the surface of cells compared to individuals with blood group B, increasing their risk of developing pancreatic cancer. Additionally, the differences in structure of the A and B antigens may provide an explanation for the difference in risk, although this has not been explored. Further research should be done to evaluate the activity of B-glycosyltransferase and compare it to the activity of A_1-glycosyltransferase to establish whether the antigen quantity could be responsible for defining the risk of pancreatic cancer development. Future studies should

separate individuals with blood type A and AB depending on whether they have the A_1 or A_2 allele to compare the risk of pancreatic cancer development in individuals with each of the A alleles separately to individuals with the other ABO phenotypes to determine which individuals are most at risk. Additionally, further research classifying individuals into their genotypes may be required to assess the impact that having one or two copies of an allele has on the risk of pancreatic cancer development, for example individuals with blood group B will either have the genotype BB or BO. This could be taken further by genotyping blood group A and AB individuals based on the presence of the A_1 or A_2 allele as well, so an individual with blood group A could have the genotype A_1A_1, A_1O, A_2A_2, A_2O, or A_1A_2. Initial studies in these areas have been conducted, however, results need to be validated with additional studies and further meta-analyses should be performed.

Glycosyltransferase activity controls the formation of ABO antigens on cell surfaces of not just red blood cells, but other tissues such as the pancreas (Franchini and Lippi, 2015). Studies have shown that ABO antigens may be important in the mediation of membrane signalling and intracellular adhesion, essential processes for the progression and metastasis of cancerous cells, as well as immunosurveillance (Le Pendu *et al*., 2001). It has been determined that the expression of ABO antigens on the surface of pancreatic cancer cells are different to the expression on normal pancreatic cells, therefore, alterations of these molecules by glycosyltransferases could be preferential for tumorigenesis (Hakomori, 1999). It may be this modification of antigen expression, caused by an alteration in glycosyltransferase specificity, that induces cancer development through increased proliferation signals and increased cell motility. As no glycosyltransferases are produced in individuals with blood group O, no antigens are present and so no modifications can be made to enhance malignancy, which may explain why blood group O individuals are less at risk of pancreatic cancer development compared to individuals with blood groups A, B, and AB who all produce transferases and have ABO antigens that can be modified to promote tumorigenesis.

Genome wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) within the *ABO* gene that links ABO blood group to levels of inflammatory mediators that regulate immune cell recruitment and inflammation (Barbalic *et al*., 2010). The evidence shows reduced levels of soluble intracellular adhesion molecule-1 (sICAM-1) and soluble P-selectin in individuals with the A_1 allele (Paré *et al*., 2008; Barbalic *et al*., 2010). ICAM-1 on the surface of the endothelium acts a receptor for LFA-1, a leukocyte integrin, and enables leukocyte attachment and diapedesis across the endothelial cells, subsequently causing inflammation. sICAM-1 binds to LFA-1, inhibiting leukocyte adhesion to ICAM-1 on the endothelium (Paré *et al*., 2008). Therefore, a reduction in sICAM-1 seen in blood group A individuals would increase interaction between LFA-1 and ICAM-1 on endothelial cells and stimulate a greater inflammatory response. The mechanism responsible could involve leukocyte interaction with the A antigen on endothelial surfaces, causing leukocytes to bind to P-selectin and ICAM-1 more strongly which prevents cleavage of these adhesion molecules into circulation, therefore reducing sICAM-1 and soluble P-selectin levels and increasing leukocyte adhesion and inflammation (Barbalic *et al*., 2010). These results could suggest that individuals with blood group A have an increased inflammatory response, suggesting chronic inflammation as a mechanism by which ABO blood group is linked to pancreatic cancer development, although the precise process by which this occurs is unknown.

Chronic inflammatory conditions have been linked to tumorigenesis through an extensive number of studies (Mantovani *et al*., 2008). In the case of pancreatic cancer, chronic pancreatitis has been found to predispose individuals to pancreatic cancer development (Raimondi *et al*., 2010) which may, in part, be due to several pro-inflammatory cytokines such as TNFα, IL-8, and IL-1 that are secreted following continuous damage and repair of the pancreas (Manohar *et al*., 2017). The results of another GWAS found associations between SNPs at the ABO locus and levels of TNFα, providing further evidence that certain ABO phenotypes may initiate or exacerbate pancreatitis, increasing the risk of pancreatic cancer (Melzer *et al*., 2008). TNFα upregulates the transcription factor NF-kB, causing activation of the NF-kB signalling pathway which has frequently been linked to tumorigenesis due its role in upregulating the expression anti-apoptotic genes, such as Bcl-2, and increasing the production of mitogenic factors, such as cyclin D1 (Garcea *et al*., 2005). Further studies are required to confirm the potential influence of ABO phenotypes on inflammation and chronic pancreatitis and the subsequent development of pancreatic cancer. So far studies have only linked blood group A with an increased inflammatory response which provides a possible explanation as to why blood group A individuals were found to be more at risk of pancreatic cancer development compared to other ABO phenotypes in this meta-analysis, but does not explain why individuals with blood groups B and AB were found to have an increased risk of pancreatic cancer compared to blood group O. It is likely due to the involvement of other mechanisms, but further research is needed to determine this. If blood group A is associated with an increased inflammatory response as studies suggest, it is expected that the risk of developing other types of cancer, not just pancreatic cancer, will be higher in this population also. This is supported by several case-control studies and meta-analyses that have identified that individuals with blood group A have a significantly increased risk of developing cancers such as gastric (Wang *et al*., 2012c; Yu *et al*., 2020), breast (Miao *et al*., 2014; Meo *et al*., 2017), and colorectal cancer (Zhang *et al*., 2014) compared to all other ABO blood group phenotypes; providing support that blood group A may be involved in increasing systemic inflammation, hence increasing the risk of developing numerous cancer types, including pancreatic cancer.

A large of number of participants across several countries and continents were included in this meta-analysis which makes the results highly generalisable and does not limit their application to specific ethnicities or populations. However, participants from South America and Africa were not represented in any included studies and so further research involving individuals from populations within these countries may be beneficial to see how these results compare to those obtained from other countries. The inclusion of different populations from several countries and ethnicities may explain the variance in results between some studies included in the meta-analysis as there are differing frequencies of each ABO phenotype between these populations. Additionally, the low global frequency of blood groups AB and B may be responsible for this variance as these phenotypes could have been underrepresented in the control groups of the studies. Alternatively, the variance in results may have been caused by the small number of pancreatic cancer cases reported by some studies. Therefore, it is important that more studies are performed involving more pancreatic cancer cases to determine the effect of ABO phenotypes, particularly AB and B, on risk of pancreatic cancer.

During the literature search, access to the full version of a few research papers was not available due to restrictions of subscriptions to certain journals, this could have

resulted in search bias and selection bias. Access to these papers would have been beneficial as they could have provided further studies and participants for inclusion in the meta-analysis, increasing the strength and validity of the results. It is also important to mention that although there appeared to be no publication bias between the studies included in the meta-analysis, studies tend not to be published if they are small and obtain insignificant results, so there is still a risk of publication bias.

A potential limitation of this meta-analysis is that the source of the healthy control group used by some of the included case-control studies may not be ideal in terms of representativeness. For example, the distribution of a particular ABO blood type may be misrepresented if blood donors were used because donors of a certain blood phenotype type may be preferred, such as the universal donors belonging to blood group O. Additionally, because of the association of ABO phenotypes with numerous diseases, it may be that there are more donors with an ABO phenotype linked to a particular disease in order to provide blood for transfusions, this would cause a bias in ABO distribution in the control group. Similarly, studies that used non-cancer related hospital patients may also have distribution bias as these patients may be in hospital for conditions or diseases that are also linked to ABO phenotype, increasing the proportion of that blood type in the control group. The ABO blood group distribution in the control group needs to be representative of the population, therefore the ideal healthy control group would be a random selection of the general population or matched control based on age, gender, and ethnicity. Despite this, many studies included in this meta-analysis did determine that the proportion of participants with each phenotype in the control groups were consistent with the proportion seen in the general population, therefore suggesting that the results are representative of the wider population and were not influenced by the source of the control group.

Most of the studies included in the meta-analysis had determined participant's ABO phenotype through serologic testing or had consensually obtained this information from hospital records. However, in the study by Wolpin *et al*. (2009), the participant's ABO phenotype was self-reported. Although the participants in this study were healthcare professionals and it was expected that they would be able to accurately report their blood type, an internal validation study conducted on 98 participants found that approximately 10% had incorrectly reported their ABO phenotype. If this proportion of participants had inaccurately reported their blood group within the entire cohort of 107,503 participants, approximately 10,000 reports of phenotype would be incorrect, potentially impacting the validity of the results obtained and affecting the accuracy of this meta-analysis. However, the authors of the study noted that with 90% of participants accurately reporting ABO phenotype, the results were unlikely to be influenced by measurement error.

A further limitation of this meta-analysis is that due to there being four ABO phenotypes, there were subsequently four comparator groups in the analysis for the risk of pancreatic cancer development to be compared between individuals of different ABO blood group phenotypes; this meant that multiple RevMan analyses were conducted to collect data. By doing this there was an increased probability of false positive results occurring. This potential issue could have been overcome by comparing the risk of pancreatic cancer development in individuals with one ABO phenotype to the risk in individuals with all other ABO phenotypes as a combined group, for example blood group A compared to non-A, O compared to non-O etc., rather than compared to each of the other ABO phenotypes individually. This method

would reduce the risk of an event occurring by chance but would not allow for a comparison of pancreatic cancer risk between each of the ABO phenotypes individually. The analysis method implemented in this meta-analysis has not been used in many other studies and provides more data on which individuals are most and least at risk of pancreatic cancer development based on their ABO phenotype. This information could be important to consider following the establishment of a UK pancreatic cancer screening programme as individuals with the highest risk ABO phenotype could potentially be invited for screening. Many other studies have only been able to conclude that non-O individuals are more at risk of pancreatic cancer with no differentiation between the risk of each of the non-O phenotypes separately. From this, all non-O individuals would be considered to have a high-risk phenotype, however it would not be feasible to include all non-O individuals in a screening programme. This meta-analysis determined that individuals with blood group A are significantly more at risk of pancreatic cancer development compared to all other ABO phenotypes, therefore, only individuals with blood group A would need to be considered for pancreatic cancer screening. Although individuals with blood type A are more at risk of developing pancreatic cancer, this factor alone is unlikely to require an individual to undergo regular screening for the malignancy. However, ABO phenotype could be used in conjunction with other risk factors, such as genetic predispositions and age, to calculate a risk score for an individual, where those that are found to be at high risk are included in pancreatic cancer screening programmes within the UK. Such screening programmes have not yet been developed but are currently in early stages of trial and evaluation in target individuals, for example those with family history of pancreatic cancer, and identify various biomarkers of pancreatic cancer. One large research study that is underway is the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC), through which people who have a strong family history of pancreatic cancer may be able to be screened (Pancreatic Cancer UK, 2021). Screening has been used to detect premalignant neoplasms to prevent development into invasive tumours but have not been used to detect early stages of pancreatic cancer. Development of screening tests that can identify both premalignant and early-stage cancers that can be treated are essential, as is the need to screen the most at-risk individuals in order to reduce both the incidence and mortality of pancreatic cancer (Rawla *et al*., 2019).

Conclusion

In conclusion, the results of this meta-analysis suggests that individuals with blood group A have a significantly increased risk of pancreatic cancer development compared to individuals with blood groups B, AB, and O, whereas individuals with blood group O are significantly less at risk of pancreatic cancer development compared to individuals with blood groups A, B, and AB. There is no significant difference in risk of pancreatic cancer development between individuals with blood group B and blood group AB. The wider implications of these findings make this study one of significance. From the results, it can be suggested that ABO phenotype should be considered and used in conjunction with other known risk factors of pancreatic cancer to influence the identification of high-risk individuals that may be eligible for future pancreatic cancer screening programmes in order to reduce the incidence and mortality rates associated with this disease. Further functional studies are required to definitively determine the mechanism by which ABO blood group phenotypes can promote tumorigenesis to better understand the complex aetiology and pathogenesis of pancreatic cancer.

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References
Aird, I., Lee, D. and Roberts, J. (1960). ABO blood groups and cancer of oesophagus, cancer of pancreas, and pituitary adenoma. *British Medical Journal,* 1(5180), pp.1163-1166.

Amundadottir, L., Kraft, P., Stolzenberg-Solomon, R., Fuchs, C., Petersen, G., Arslan, A., Bueno-de-Mesquita, H., Gross, M., Helzlsouer, K., Jacobs, E., LaCroix, A., Zheng, W., Albanes, D., Bamlet, W., Berg, C., Berrino, F., Bingham, S., Buring, J., Bracci, P., Canzian, F., Clavel-Chapelon, F., Clipp, S., Cotterchio, M., de Andrade, M., Duell, E., Fox, J., Gallinger, S., Gaziano, J., Giovannucci, E., Goggins, M., González, C., Hallmans, G., Hankinson, S., Hassan, M., Holly, E., Hunter, D., Hutchinson, A., Jackson, R., Jacobs, K., Jenab, M., Kaaks, R., Klein, A., Kooperberg, C., Kurtz, R., Li, D., Lynch, S., Mandelson, M., McWilliams, R., Mendelsohn, J., Michaud, D., Olson, S., Overvad, K., Patel, A., Peeters, P., Rajkovic, A., Riboli, E., Risch, H., Shu, X., Thomas, G., Tobias, G., Trichopoulos, D., Van Den Eeden, S., Virtamo, J., Wactawski-Wende, J., Wolpin, B., Yu, H., Yu, K., Zeleniuch-Jacquotte, A., Chanock, S., Hartge, P. and Hoover, R. (2009). Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nature Genetics*, 41(9), pp.986-90.

Anstee, D. (2010). The relationship between blood groups and disease. *Blood,* 115(23), pp.4635-4643.

Antwi, S., Bamlet, W., Pedersen, K., Chaffee, K., Risch, H., Shivappa, N., Steck, S., Anderson, K., Bracci, P., Polesel, J., Serraino, D., La Vecchia, C., Bosetti, C., Li, D., Oberg, A., Arslan, A., Albanes, D., Duell, E., Huybrechts, I., Amundadottir, L., Hoover, R., Mannisto, S., Chanock, S., Zheng, W., Shu, X., Stepien, M., Canzian, F., Bueno-de-Mesquita, B., Quirós, J., Zeleniuch-Jacquotte, A., Bruinsma, F., Milne, R., Giles, G., Hébert, J., Stolzenberg-Solomon, R. and Petersen, G. (2018). Pancreatic cancer risk is modulated by inflammatory potential of diet and ABO genotype: a consortia-based evaluation and replication study. *Carcinogenesis*, 39(8), pp.1056-1067.

Barbalic, M., Dupuis, J., Dehghan, A., Bis, J., Hoogeveen, R., Schnabel, R., Nambi, V., Bretler, M., Smith, N., Peters, A., Lu, C., Tracy, R., Aleksic, N., Heeriga, J., Keaney Jr, J., Rice, K., Lip, G., Vasan, R., Glazer, N., Larson, M., Uitterlinden, A., Yamamoto, J., Durda, P., Haritunians, T., Psaty, B., Boerwinkle, E., Hofman, A., Koenig, B., Jenny, N., Witteman, J., Ballantyne, C. and Benjamin, E. (2010). Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. *Human Molecular Genetics,* 19(9), pp.1863-1872.

Ben, Q., Wang, K., Yuan, Y. and Li, Z. (2011). Pancreatic cancer incidence and outcome in relation to ABO blood groups among Han Chinese patients: A case-control study. *International Journal of Cancer,* 128(5), pp.1179-1186.

Calafell, F., Roubinet, F., Ramírez-Soriano, A., Saitou, N., Bertranpetit, J. and Blancher, A. (2008). Evolutionary dynamics of the human *ABO* gene. *Human Genetics,* 124, pp.123-135.

Daniels, G. (2008). Human blood groups. 2nd ed. Oxford: Blackwell Publishing Company. pp.1-25.

De La Cruz, M., Young, A. and Ruffin, M. (2014). Diagnosis and management of pancreatic cancer. *American Family Physician,* 89(8), pp.626-632.

Egawa, N., Lin, Y., Tabata, T., Kuruma, S., Hara, S., Kubota, K. and Kamisawa, T. (2013). ABO blood type, long-standing diabetes, and the risk of pancreatic cancer. *World Journal of Gastroenterology,* 19(16), pp.2537-2542.

El Jellas, K., Hoem, D., Hagen, K., Kalvenes, M., Aziz, S., Steine, S., Immervoll, H., Johansson, S. and Molven, A. (2017). Associations between ABO blood groups and pancreatic ductal adenocarcinoma: influence on resection status and survival. *Cancer Medicine*, 6(7), pp.1531-1540.

Engin, H., Bilir, C., Üstün, H. and Gökmen, A. (2012). ABO blood group and the risk of pancreatic cancer in a Turkish population in Western Blacksea region. *Asian Pacific Journal of Cancer Prevention,* 13(1), pp.131-133.

Garcea, G., Dennison, A., Steward, W. and Berry, D. (2005). Role of inflammation in pancreatic carcinogenesis and the implications for future therapy, *Pancreatology.* 5, pp.514-52.

Gong, Y., Ynag, Y., Zhang, X., Su, M., Wang, J., Han, J. and Guo, M. (2012). ABO blood type, diabetes and risk of gastrointestinal cancer in northern China. *World Journal of Gastroenterology,* 18(6), pp.563-569.

Greer, J., Yazer, M., Raval, J., Barmada, M.., Brand, R. and Whitcomb, D. (2010). Significant association between ABO blood group and pancreatic cancer. *World Journal of Gastroenterology*, 16(44), pp.588-5591.

Franchini, M., Liumbruno, G. and Lippi, G. (2016). The prognostic value of ABO blood group in cancer patients. *Blood Transfusion,* 14(5), pp.434-440.

Franchini, M. and Lippi, G. (2015). The intriguing relationship between the ABO blood group, cardiovascular disease, and cancer. *BioMed Central Medicine,* 13, pp.7.

Hakomori, S. (1999). Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. *Biochimica et Biophysica Acta,* 1473, pp.247-266.

Hidalgo, M., Cascinu, S., Kleeff, J., Labianca, R., Löhr, J., Neoptolemos, J., Real, F., Laethem, J. and Heinemann, V. (2015). Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology,* 15(1), pp.8-18.

Hsiao, L., Liu, N., You, S. and Hwang, L. (2015). ABO blood group and the risk of cancer among middle-aged people in Taiwan. *Asia-Pacific Journal of Clinical Oncology,* 11, E31-36.

Huang, J., Wang, R., Gao, Y. and Yuan, J. (2017). ABO blood type and the risk of cancer – Findings from the Shanghai Cohort Study. *PLoS ONE,* 12(9), e0184295.

Iodice, S., Maisonneuve, P., Botteri, E., Sandri, M. and Lowenfels, A. (2010). ABO blood group and cancer. *European Journal of Cancer,* 46(18), pp.3345-3350.

Klein, A., Lindström, S., Mendelsohn, J., Steplowski, E., Arslan, A., Bueno-de-Mesquita, H., Fuchs, C., Gallinger, S., Gross, M., Helzlsouer, K., Holly, E., Jacobs, E., Lacroix, A., Li, D., Mandelson, M., Olson, S., Petersen, G., Risch, H., Stolzenberg-Solomon, R., Zheng, W., Amundadottir, L., Albanes, D., Allen, N., Bamlet, W., Boutron-Ruault, M., Buring, J., Bracci, P., Canzian, F., Clipp, S., Cotterchio, M., Duell, E., Elena, J., Gaziano, J., Giovannucci, E., Goggins, M., Hallmans, G., Hassan, M., Hutchinson, A., Hunter, D., Kooperberg, C., Kurtz, R., Liu, S., Overvad, K., Palli, D., Patel, A., Rabe, K., Shu, X., Slimani, N., Tobias, G., Trichopoulos, D., Van Den Eeden, S., Vineis, P., Virtamo, J., Wactawski-Wende, J., Wolpin, B., Yu, H., Yu, K., Zeleniuch-Jacquotte, A., Chanock, S., Hoover, R., Hartge, P. and Kraft, P. (2013). An absolute risk model to identify individuals at elevated risk for pancreatic cancer in the general population. *PLoS ONE*, 8(9), e72311.

Kos, F., Civelek, B., Seker, M., Arik, Z., Aksoy, S., Uncu, D., Ozdemir, N. and Zengin, N (2012). Is there an association between blood group and survival in pancreatic cancer? *Asian Pacific Journal of Cancer Prevention*, 13(12), pp.6151-3.

Lennon, A., Klein, A. and Goggins, M. (2010). ABO blood group and other genetic variants associated with pancreatic cancer. *Genome Medicine,* 2(6), pp.1-5.

Le Pendu, J., Marionneau, S., Cailleau-Thomas, A., Rocher, J., Le Maollac-Vaidye, M. and Clément, M. (2001). ABH and Lewis histo-blood group antigens in cancer. *APMIS,* 109(1), pp.9-26.

Li, D., Pise, M., Overman, M., Liu, C., Tang, H., Vadhan-Raj, S. and Abbruzzese, J. (2015). ABO non-O type as a risk factor for thrombosis in patients with pancreatic cancer. *Cancer Medicine,* 4(11), pp.1651-1658.

Li, S., Zhou, C., Liao, R., Xiong, L., Weng, N., Zhao, Y., Mason, C., Gou, H., Yi, C. and Zhu, Q. (2020). ABO blood type, smoking status, other risk factors and prognosis of pancreatic ductal adenocarcinoma. *Medicine (Baltimore),* 99(14), E19413.

Li, X., Xu, H. and Gao, P. (2018). ABO blood group and diabetes mellitus influence the risk for pancreatic cancer in a population from China. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research,* 24, pp.9392-9398.

Liu, M., Ji, S., Xu, W., Liu, W., Qin, Y., Xiang, J., Hu, Q., Sun, Q., Zhang, Z., Xu, X., and Yu, X. (2019). ABO blood group and the risk of pancreatic neoplasms in Chinese Han population: A study at shanghai pancreatic cancer institute. *Pancreas*, 48(9), e65–66.

Macafee, A. (1964). ABO blood groups and carcinoma of pancreas. *The Ulster Medical Journal,* 33(2), pp.129-131.

Manohar, M., Verma, A., Venkateshaiah, S., Sander, N. and Mishra, A. (2017). Pathogenic mechanisms of pancreatitis. *World Journal of Gastrointestinal Pharmacology and Therapeutics,* 8(1), pp.10-15.

Mantovani, A., Allavena, P., Sica, A. and Balkwill, F. (2008). Cancer-related inflammation. *Nature,* 454, pp.436-444.

Melzer, D., Perry, J., Hernandez, D., Corsi, A., Stevens, K., Rafferty, I., Lauretani, F., Murray, A., Gibbs, J., Paolisso, G., Rafiq, S., Simon-Sanchez, J., Lango, H., Scholz, S., Weedon, M., Arepalli, S., Rice, N., Washecka, N., Hurst, A., Britton, A., Henley, W., van de Leemput, J., Li, R., Newman, A., Tranah, G., Harris, T., Panicker, V., Dayan, C., Bennett, A., McCarthy, M., Ruokonen, A., Jarvelin, M., Guralnik, J., Bandinelli, S., Frayling, T., Singleton, A. and Ferrucci, L. (2008). A genome-wide association study identifies protein quantitative trait loci (pQTLs). *PLoS Genetics,* 4(5), E10000072.

Meo, S., Suraya, F., Jamil, B., Al Rouq, F., Meo, A., Sattar, K., Ansari, M. and Alasiri, S. (2017). Association of ABO and Rh blood groups with breast cancer. *Saudi Journal of Biological Sciences,* 24(7), pp.1609-1613.

Miao, S., Zhou, W., Chen, L., Wang, S. and Liu, X. (2014). Influence of ABO blood group and rhesus factor on breast cancer risk: A meta-analysis of 9665 breast cancer patients and 244768 controls. *Asia-Pacific Journal of Clinical Oncology,* 10, pp.101-108.

Mizrahi, J., Surana, R., Valle, J. and Shroff, R. (2020). Pancreatic cancer. *The Lancet,* 395(10242), pp.2008-2020.

Nakao, M., Matsuo, K., Honsono, S., Ogata, S., Ito, H., Watanabe, M., Mizuno, N., Iida, S., Sato, S., Yatabe, Y., Yamao, K., Ueda, R., Tajima, K. and Tanaka, H. (2011). *ABO* blood group alleles and the risk of pancreatic cancer in a Japanese population. *Cancer Science,* 102(5), pp.1076-1080.

Newell, G., Gordon, J., Monlezun, A. and Horwitz, J. (1974). ABO blood groups and Cancer. *Journal of the National Cancer Institute,* 52(5), pp.1425-1430.

Pancreatic Cancer UK. (2021). Screening for pancreatic cancer. Available at: https://www.pancreaticcancer.org.uk/information/screening-for-pancreatic-cancer/#:~:text=There%20is%20no%20NHS%20screening,Cancer%20(EUROPAC)%20research%20study. Accessed: 1st Feb 2021.

Paré, G., Chasman, D., Kellogg, M., Zee, R., Rifai, N., Badola, S., Miletich, J. and Ridker, P. (2008). Novel association of ABO histo-blood group antigen with soluble ICAM-1: Results of a genome-wide association study of 6,578 women. *PLoS Genetics,* 4(7), E1000118.

Pelzer, U., Klein, F., Bahra, M., Sinn, M., Dörken, B., Neuhaus, P., Meyer, O. and Riess, H. (2013). Blood group determinates incidence for pancreatic cancer in Germany. *Frontiers in Physiology,* 24(4), pp.118.

Rahbari, N., Bork, U., Hinz, U., Leo, A., Kirchberg, J., Koch, M., Büchler, M. and Weitz, J. (2012). AB0 blood group and prognosis in patients with pancreatic cancer. *BioMed Central Cancer*, 12(1), pp.319.

Raimondi, S., Lowenfels, A., Morselli-Labate, A., Maisonneuve, P. and Pezzilli, R. (2010). Pancreatic cancer in chronic pancreatitis: aetiology, incidence, and early detection. *Best Practice in Research and Clinical Gastroenterology,* 24, pp.349-358.

Rawla, P., Sunkara, T. and Gaduputi, V. (2019). Epidemiology of pancreatic cancer: Global trends, etiology and risk factors. *World Journal of Oncology,* 10(1), pp.10-27.

Risch, H., Lu, L., Wang, J., Zhang, W., Ni, Q., Gao, Y. and Yu, H. (2013). ABO blood group and risk of pancreatic cancer: A study in Shanghai and meta-analysis. *American Journal of Epidemiology*, 177(12), pp.1326-1337.

Risch, H., Tu, H., Lu, L. and Kidd, M. (2010). ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: A case-control study. *Journal of the National Cancer Institute,* 102(7), pp.502-505.

Risch, H., Yu, H., Lu, L. and Kidd, M. (2015). Detectable symptomatology preceding the diagnosis of pancreatic cancer and absolute risk of pancreatic cancer diagnosis. *American Journal of Epidemiology,* 182(1), pp.26-34.

Rizzato, C., Campa, D., Pezzilli, R., Soucek, P., Greenhalf, W., Capurso, G., Talar-Wojnarowska, R., Heller, A., Jamroziak, K., Khaw, K. and Key, T. (2013). ABO blood groups and pancreatic cancer risk and survival: Results from the PANcreatic Disease ReseArch (PANDoRA) consortium. *Oncology Reports*, 29(4), pp.1637-1644.

Rummel, S. and Ellsworth, R. (2016). The role of the histoblood ABO group in cancer. *Future Science OA,* 2(2), FSO107.

Storry, J. and Olsson, M. (2009). The ABO blood group system revisited: A review and update. *Immunohematology,* 25(2), pp.48-59.

Sun, W., Wen, C., Lin, J., Wen, C., Pu, X., Huang, M., Tsai, M., Tsao, C., Wu, X. and Chow, W. (2015). ABO blood types and cancer risk – A cohort study of 339,432 subjects in Taiwan. *Cancer Epidemiology*, 39(2), pp.150-156.

Sung, H., Ferlay, J., Siegel, R., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality for 36 cancers in 185 countries. *A Cancer Journal of Clinicians.*

Svensson, L., Rydberg, L., de Mattis, L. and Henry, S. (2009). Blood group A_1 and A_2 revisited: An immunochemical analysis. *Vox Sanguinis,* 96(1), pp.56-61.

Tanaka, Y., Kumagi, T., Terao, T., Kuroda, T., Yokota, T., Azemoto, N., Imamura, Y., Uesugi, K., Kisaka, Y., Shibata, N., Koizumi, M., Ohno, Y., Kanemitsu, K., Yukimoto, A., Tange, K., Nishiyama, M., Miyake, T., Miyata, H., Ishii, H., Abe, M. and Hiasa, Y. (2020). ABO Blood Type and the Long-term Outcomes of Pancreatic Cancer. *Internal Medicine Journal*, 59(6), pp.761-768.

Vasan, S., Hwang, J., Rostgaard, K., Nyrén, Ullum, H., Pedersen, O., Erikkstrup, C., Melbye, M., Hjalgrim, H., Pawitan, Y. and Edgren, G. (2016). ABO blood group and risk of cancer: A register-based cohort study of 1.6 million blood donors. *Cancer Epidemiology,* 44, pp.40-43.

Wang, D., Chen, D., Ren, C., Wang, Z., Qiu, M., Luo, H., Zhang, D., Wang, F., Li, Y. and Xu, R. (2012a). ABO blood group, hepatitis B viral infection and risk of pancreatic cancer. *International Journal of Cancer*, 131(2), pp.461-468.

Wang, D., Wang, Z., Zhang, L., Qiu, M., Luo, H., Ren, C., Zhang, D., Wang, F., Li, Y. and X, R. (2012b). Are the risk factors associated with outcomes in pancreatic cancer?. *PLoS One,* 7(7), E41984.

Wang, H., Liu, J., Xia, G., Lei, S., Huang, X. and Huang, X. (2020). Survival of pancreatic cancer patients is negatively correlated with age at diagnosis: a population-based retrospective study. *Scientific Reports,* 10(7048).

Wang, Z., Lei, L., Ji, J., Zhang, J., Yan, M., Zhang, J., Liu, B., Zhu, Z. and Yu, Y. (2012c). ABO blood group system and gastric cancer: A case-control study and meta-analysis. *International Journal of Molecular Sciences,* 13, pp.13308-13321.

Wolpin, B., Chan, A., Hartge, P., Chanock, S., Kraft, P., Hunter, D., Giovannucci, E. and Fuchs, C. (2009). ABO blood group and the risk of pancreatic cancer. *Journal of the National Cancer Institute*, 101(6), pp.424-431.

Wolpin, B., Kraft, P., Gross, M., Helzlsouer, K., Bueno-de-Mesquita, H., Steplowski, E., Stolzenberg-Solomon, R., Arslan, A., Jacobs, E., Lacroix, A., Petersen, G., Zheng, W., Albanes, D., Allen, N., Amundadottir, L., Anderson, G., Boutron-Ruault, M., Buring, J., Canzian, F., Chanock, S., Clipp, S., Gaziano, J., Giovannucci, E., Hallmans, G., Hankinson, S., Hoover, R., Hunter, D., Hutchinson, A., Jacobs, K., Kooperberg, C., Lynch, S., Mendelsohn, J., Michaud, D., Overvad, K., Patel, A., Rajkovic, A., Sanchéz, M., Shu, X., Slimani, N., Thomas, G., Tobias, G., Trichopoulos, D., Vineis, P., Virtamo, J., Wactawski-Wende, J., Yu, K., Zeleniuch-Jacquotte, A., Hartge, P. and Fuchs, C. (2010a). Pancreatic cancer risk and ABO blood group alleles: Results from the pancreatic cancer cohort consortium. *Cancer research*, 70(3), pp.1015–1023.

Wolpin, B., Kraft, P., Xu, M, Steplowski, E., Olsson, M., Arslan, A., Bueno-de-Mesquita, H., Gross, M., Helzlsouer, K., Jacobs, E., Lacroix, A., Petersen, G., Stolzenberg-Solomon, R., Zheng, W., Albanes, D., Allen, N., Amundadottir, L., Austin, M., Boutron-Ruault, M., Buring, J., Canzian, F., Chanock, S., Gaziano, J., Giovannucci, E., Hallmans, G., Hankinson, S., Hoover, R., Hunter, D., Hutchinson, A., Jacobs, K., Kooperberg, C.,Mendelsohn, J., Michaud, D., Overvad, K., Patel, A., Rajkovic, A., Sanchéz, M., Sansbury, L., Shu, X., Slimani, N., Tobias, G., Trichopoulos, D., Vineis, P., Visvanathan, K., Virtamo, J., Wactawski-Wende, J., Watters, J., Yu, K., Zeleniuch-Jacquotte, A., Hartge, P. and Fuchs, C. (2010b). Variant ABO blood group alleles, secretor status and risk of pancreatic cancer: Results from the Pancreatic Cancer Cohort Consortium. *Cancer Epidemiology, Biomarkers and Prevention,* 19(12), pp.3140-3149.

Woo, S., Joo, J., Lee, W., Park, S., Han, S., Kim, T., Koh, Y., Kim, H. and Hong, E. (2013). Risk of pancreatic cancer in relation to ABO blood group and hepatitis C virus infection in Korea: A case-control study. *Journal of Korean Medical Science*, 28(2), pp.247–251.

Xu, H., Cheng, J., Zhang, W., Wang, J., Yu, H., Ni, Q., Risch, H. and Gao, Y. (2014). Re-evaluation of ABO gene polymorphisms detected in a genome-wide association study and risk of pancreatic ductal adenocarcinoma in a Chinese population. *Chinese Journal of Cancer,* 33(2), pp.68-73.

Yu, H., Xu, N., Li, Z., Xia, H., Ren, H., Li, N., Wei, J. and Bao, H. (2020). Association of ABO blood group and risk of gastric cancer. *Scandinavian Journal of Surgery,* 109(4), pp.309-313.

Zhang, B., He, N., Huang, Y., Song, F. and Chen, K. (2014). ABO blood groups and risk of cancer: A systemic review and meta-analysis. *Asian Pacific Journal of Cancer Prevention,* 15, pp.4643-4650.

Zhou, G. and Li, Z. (2005). Clinical epidemiological research on pancreatic cancer: an analysis of 1027 cases. *World Chinese Journal of Digestion,* 13(1), pp.55-60.