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ABO blood group and cancer

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ABSTRACT

Background: ABO blood type has been associated with various malignancies, including pancreatic cancer. Our aim was to study this association using data from a hospital-based tumour registry.

Methods: From the tumour registry, we retrieved data from 15,359 cancer patients treated during 2000–2003 at the European Institute of Oncology (Milan, Italy), with defined ABO blood type. We performed a case-control analysis, comparing the distribution of ABO blood types of patients with each specific form of cancer against that of patients with other forms of cancer. We also reviewed the literature and performed a meta-analysis on the association between ABO blood group and pancreatic cancer.

Results: We observed a significantly lower frequency of blood type O in patients with exocrine pancreatic cancer compared to patients with other forms of cancer (29% versus 44%; $P < 0.001$; odds ratio (OR), 0.53; 95% confidence intervals (CI), 0.33–0.83). This association was confirmed by the meta-analysis of seven prior studies (summary relative risk, 0.79; 95% CI, 0.70–0.90). No association was found for endocrine pancreatic cancer or for cancer originating in other organs.

Conclusions: Our data suggest that the association between ABO blood group and cancer is limited to exocrine pancreas malignancy.

1. Introduction

Although the relation between ABO blood group and cancer was the subject of intensive research in the mid 1900's, there has been renewed interest after the recent publication of reports establishing an association between ABO blood group and pancreatic cancer.[1,2] Simultaneously, a genome-wide association study (GWAS) identified pancreatic cancer susceptibility loci in the ABO gene.[3] Given the lack of survival improvement during the past 30 years,[4] these recent findings on the individual predisposition to pancreatic cancer might play an important role in screening planning and clinical practice.

In order to confirm these recent findings in a different population and different setting and to assess whether the association is limited to pancreatic cancer, we studied the distribution of ABO blood group in patients with various forms of cancer using data from the tumour registry of the European Institute of Oncology (IEO). We also performed a meta-analysis of all published reports on the association between ABO blood group and pancreatic cancer to summarise the current evidence.

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2. Materials and methods

2.1. Tumour registry data

This study is based on data from the IEO Tumour Registry, a database activated in March 2006 with the aim to collect and analyse data on all those consulting at IEO, at risk of developing or already presenting with a tumour. More details on data collection, data quality control procedures and activity of the IEO Tumour Registry have been published elsewhere.[5]

For the present study, in order to deal with the most reliable and complete data in the registry, we limited the analysis to patients with a histologically proven diagnosis of cancer who received at least one treatment modality at the IEO, whether surgery or any other treatment. Information on ABO blood type was recorded as part of routine clinical care and automatically linked the tumour registry data. Overall, we analysed data from 15,359 patients who were treated for the first time at the IEO between 1999 and 2003 for a histologically proven cancer and with defined ABO blood type.

2.2. Statistical methods

We assessed the relationship between ABO blood type and each form of cancer, focusing on the effect of O versus non-O blood type on pancreatic cancer and on its histological subtypes. We excluded cancer sites with less than 20 affected patients. We performed case-control analyses defining as 'cases' patients with a particular form of cancer and 'controls' those with any other form of tumour. We used χ^2 tests to assess differences between groups, and logistic regression models adjusted for sex, age at diagnosis, smoking status and region (Northern versus Southern Italy) to estimate odds ratio (OR) and 95% confidence intervals (CI). We used the Benjamini and Hochberg approach[6] based on the false discovery rate calculation to control for multiple comparisons.

2.3. Meta-analysis

For the meta-analysis, we conducted a literature search and reviewed articles published from 1953 to February 2010 using validated search strategies[7] on PUBMED, EMBASE and Ovid MEDLINE® databases, using combinations of the following words: 'ABO blood type', 'cancer' and 'pancreas' entered as keywords and MeSh terms. We also scrutinised published papers referring to the most cited articles on the topic using ISI Web of Knowledge® Science Citation Index Expanded™ (Journal Citation Report). Finally, we reviewed the references of all relevant articles to identify additional relevant studies. The search was limited to human studies and no language or time restrictions were applied.

The aim of the meta-analysis was to study the effect of O blood type on the risk of pancreatic cancer. We included case-control and cohort studies published as original articles and

Table 1 – ABO blood group distribution of patients with invasive cancer registered in the IEO Tumour Registry.

Cancer site	Total	ABO blood group (%)				P-value[a]
		A	B	AB	O	Non-O[b] versus O
Lip oral cavity and pharynx	476	170 (36)	73 (15)	18 (4)	215 (45)	0.59
Oesophagus	63	26 (40)	2 (3)	3 (5)	32 (52)	0.27
Stomach	301	118 (40)	28 (9)	17 (6)	138 (45)	0.51
Colorectum	940	384 (41)	92 (10)	32 (3)	432 (46)	0.21
Liver and intrahepatic bile ducts	78	35 (46)	11 (14)	4 (4)	28 (36)	0.15
Gallbladder and extrahepatic bile ducts	57	19 (33)	7 (12)	4 (7)	27 (47)	0.60
Pancreas	104	53 (51)	13 (13)	4 (4)	34 (33)	0.02
– Adenocarcinoma	90	47 (52)	13 (14)	4 (4)	26 (29)	0.003
– Neuroendocrine carcinoma	14	6 (43)	0 (0)	0 (0)	8 (57)	0.42
Respiratory and intrathoracic	1730	685 (40)	188 (11)	68 (4)	789 (46)	0.15
Connective and other soft tissue	346	144 (42)	50 (15)	10 (3)	142 (41)	0.27
Non-melanoma skin	297	115 (39)	38 (13)	21 (7)	123 (41)	0.37
Melanoma	463	175 (38)	45 (10)	622 (5)	221 (48)	0.10
Breast	7208	2892 (40)	856 (12)	307 (4)	3153 (44)	0.60
Female genitary organs	1082	454 (42)	116 (11)	40 (4)	472 (44)	0.81
Prostate	719	308 (43)	74 (10)	32 (4)	305 (42)	0.39
Kidney	276	110 (40)	39 (14)	14 (5)	113 (41)	0.31
Bladder	344	160 (46)	34 (10)	13 (4)	137 (40)	0.12
Thyroid gland	290	97 (33)	37 (13)	15 (5)	141 (49)	0.11
Hodgkin lymphoma	94	31 (33)	13 (14)	5 (5)	45 (48)	0.44
Non-Hodgkin lymphoma	336	132 (39)	49 (15)	11 (3)	144 (43)	0.68
Multiple myeloma	77	28 (36)	9 (12)	6 (8)	34 (44)	0.97
Leukaemia	78	38 (49)	8 (10)	4 (5)	28 (36)	0.15
All sites	15,359	6174 (40)	1782 (12)	650 (4)	6753 (44)	
All, but pancreas	15,255	6121 (40)	1769 (12)	646 (4)	6719 (44)	
Italian general population	100%	42%	9%	3%	46%	

[a] P-value testing the differences in O group prevalence of each site when compared to all the other sites.
[b] Non-O = A + B + AB blood groups.

containing the minimum information to obtain an estimate of the relative risk, with its uncertainty. The studies had to be independent: in case of multiple reports on the same population or sub-population, we retained the estimates from the most recent or most informative report. Articles were reviewed and data were extracted and crosschecked independently by two investigators (S.I. and P.M.) and any disagreement was resolved by consensus among them. We extracted and coded from the original articles information on adjusted risk estimates or crude data, year of publication, type of study, country of the study, features of populations, ABO blood type, adjustments or matching variables used in the analysis and study design.

We used random effect models with maximum likelihood estimates rather than fixed effects models to estimate summary relative risks (SRRs) in order to take into account the heterogeneity of the risk estimates and therefore to be more conservative.[8] Homogeneity of effects across studies was assessed using the χ^2 statistic and quantified by I^2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.[9,10] Subgroup analyses were carried out to investigate potential sources of between-study heterogeneity.[11]

Sensitivity analysis was carried out in order to evaluate whether the overall result was influenced by a single or a group of studies.[12] Publication bias was evaluated by funnel plots and quantified by the Egger's test.[13,14]

All analyses were performed with SAS Software (SAS Institute Inc., Cary, NC).

3. Results

3.1. Tumour registry data

Information on ABO blood type was available for 79% of all patients referred and treated for the first time at the IEO during 1999–2003. Overall, the ABO blood group distribution of the 15,359 cancer patients was similar to that of the Italian general population[15] ($P = 0.78$): 6753 patients (44%) were blood group O, 6174 (40%) group A, 1782 (12%) group B and 650 (4%) group AB. The blood group distribution of patients with each form of cancer is reported in Table 1.

Pancreas was the only cancer site for which we observed a statistically significant different proportion of patients with blood type O (33% versus 44% for all other forms of cancer combined, $P = 0.02$). The difference was limited to the subset of patients with exocrine pancreatic cancer (adenocarcinomas) (29% versus 44%, $P = 0.003$). After adjusting for sex, age at diagnosis, smoking status and domicile area, O blood group was associated with a 47% risk reduction of exocrine pancreatic cancer (OR, 0.53; 95% CI, 0.33–0.83). We observed no difference in the frequency of O blood group for any other cancer sites, nor for the 14 patients diagnosed with endocrine pancreatic cancer ($P = 0.42$). In a subgroup analysis limited to the 90 patients with adenocarcinoma of the pancreas, the association with O blood group was not modified by sex, age, smoking status, diabetes, residence area or tumour stage (Table 2).

We did not find any relevant association for any form of cancer, when we compared the individual frequency of A, B and AB blood types. In particular, no difference was observed in the distribution of A versus non-A blood groups among gastric cancer patients (data not shown).

In a separate analysis, we investigated whether blood group was associated with stage of disease for each individual cancer sites, and found no difference in the frequency of O blood type in patients with either local, regional or distant disease at presentation (data not shown).

When applying the Benjamini and Hochberg approach for multiple comparisons,[6] the association between ABO blood

Table 2 – Characteristics of patients diagnosed with pancreatic adenocarcinomas according to blood group.

Characteristics[b]	Blood group (%)					P-value[a]
	Total	Non-O		O		
Total	90	64	(71)	26	(29)	
First primary only	75	53	(71)	22	(29)	1.00
Second primary	15	11	(73)	4	(27)	
Gender						
Women	53	40	(75)	13	(25)	0.27
Men	37	24	(65)	13	(35)	
Age at diagnosis						
<60 years	37	27	(73)	10	(27)	0.95
60–69 years	34	23	(68)	11	(32)	
⩾70 years	19	14	(74)	5	(26)	
Smoking status						
Current	13	10	(77)	3	(23)	0.29[c]
Former	16	12	(75)	4	(25)	
Never	24	15	(63)	9	(38)	
Diabetes						
Absent	71	51	(72)	20	(28)	0.77
Present	19	13	(68)	6	(32)	
Domicile[d]						
Northern Italy	69	51	(74)	18	(26)	0.29
Southern Italy	21	13	(62)	8	(38)	
Tumour location						
Head	53	38	(72)	15	(28)	0.87[e]
Body and/or tail	32	24	(75)	8	(25)	
Unspecified	5	2	(40)	3	(60)	
Tumour size (pT)						
pT2	6	6	(100)	0	(0)	0.64
pT3	21	12	(80)	3	(20)	
pT4	2	2	(100)	0	(0)	
pTx	45	30	(67)	15	(33)	
Nodal status (pN)						
pN0	10	9	(90)	1	(10)	0.42
pN+	13	10	(77)	3	(23)	
Metastasis (pM)						
pM0	8	7	(88)	1	(13)	0.65
pM+	31	22	(71)	9	(29)	
Tumour grade						
G1–G2	14	10	(71)	4	(29)	0.70
G3	18	14	(78)	4	(22)	

[a] χ^2 or Fisher exact test P-value as appropriate.
[b] Data was not available for all patients.
[c] Ever versus never smokers.
[d] Northern regions: including Tuscany, Marches and Umbria and regions located above them.
[e] Cancer of the head of pancreas versus body/tail.

group and pancreatic adenocarcinoma remained statistically significant.

3.2. *Meta-analysis*

Details on search strategy and data extrapolation are described in Fig. 1. Table 3 describes the main characteristics of the 12 studies identified from the literature search, which reported on the association between ABO blood group and pancreatic cancer.[1,16–26] Two studies[16,17] were not independent from that from Vogel and Krüger[18] and were evaluated only in the sensitivity analysis. Ten independent studies with 5403 pancreatic cancer cases and 125,893 healthy controls were included in the meta-analysis. Overall, pancreatic cancer risk is significantly decreased in patients with O blood type (SRR, 0.79; 95% CI, 0.70–0.90; Fig. 2) in agreement with our findings and similar to findings from the two more recent reports.[1,2] The risk estimates were rather heterogeneous (I^2, 61%; $P < 0.01$). In a sensitivity analysis, exclusion of the only article not written in English[24] reduced the heterogeneity (I^2, 35%; $P = 0.14$) and slightly decreased the summary risk estimate (SRR, 0.76; 95% CI, 0.69–0.83). Exclusion of the study by Kokic and colleagues[22] which reported a strong protective effect of blood type O Rhesus+ did not modify the summary risk estimate (SRR, 0.80; 95% CI, 0.97–0.91). We used results from a pooled analysis published in 1970 and based on 13 early studies[18] as a summary of all earlier reports. Substitution of this pooled study by two representative early but more detailed studies[16,17] did not alter the results (SRR, 0.80; 95% CI, 0.71–0.90, I^2, 59%; $P < 0.01$). No indication of publication bias was found when assessing O group effect on pancreatic cancer: *P*-value from weighted Egger's test for funnel plot was 0.35.

4. Discussion

In the IEO Tumour Registry, exocrine pancreatic cancer was the only form of tumour that exhibited a significant difference in the proportion of patients with blood type O compared to other forms of cancer. Overall, O blood group was associated with a 47% risk reduction of exocrine pancreatic cancer. This association was not modified by established risk factors for pancreatic cancer, including age, medical history of diabetes and cigarette smoking, but the lack of significant interaction may be due to the limited number of patients in each stratum. The risk reduction for the O blood group appeared stronger in the IEO Tumour Registry (47%) than in the meta-analysis (20%), but the two risk estimates were not significantly different, with overlapping confidence intervals. The stronger risk reduction observed in our study could again be attributable to the limited number of pancreatic cancer patients.

We assessed the relationship between ABO blood type and pancreatic cancer using a case-control methodology where 'controls' were all non-pancreatic cancers registered in the tumour registry. This analysis could be biased if blood type was associated with the reference cancer group (all but pancreas). However, selecting a broad range of malignancies (21 sites) for the comparison group minimised this risk. In addition, the blood group distribution of control patients was similar to that of the general Italian population.[15] Our results are in agreement with recent reports[1,2] and with the meta-analysis which indicate a 21% decrease risk of pancreatic cancer risk in patients inheriting an O blood type.

As a possible explanation, recent extensive GWAS studies have identified association between single nucleotide

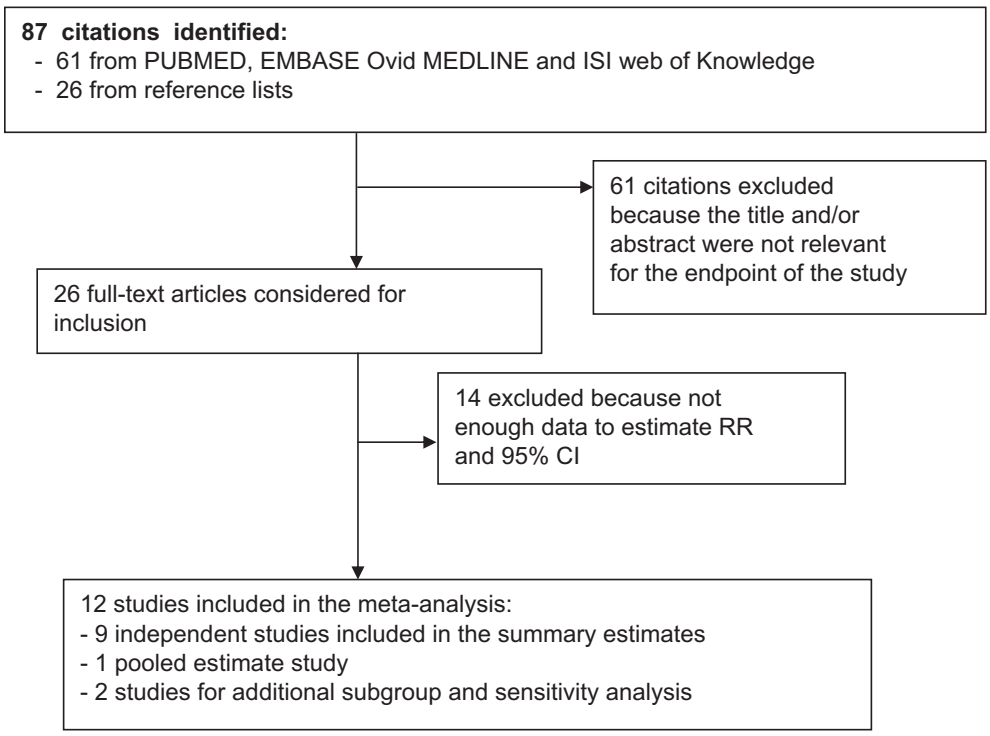

Fig. 1 – Flow chart of the selection of the studies.

Table 3 – Characteristics of the studies included in the meta-analysis on ABO blood group and pancreatic cancer.

Author, publication year	Reference	Country	Study type	Cases		Controls		Cancer diagnosis	Source of controls
				Type O	Non-O	Type O	Non-O		
Aird et al., 1960	[16]	UK	CC	272	348	29,907	32,893	Histological	Voluntary donors
Macafee, 1964	[17]	UK	CC	56	63	5522	5805	Histological	Voluntary donors
Vogel and Krüger, 1968 [a]	[18]	Mixed	PA	817[b]	–	108,408[b]	–	NA	NA
Newell et al., 1974	[19]	USA	CC	60	77	2394	2601	Histological	Voluntary donors
Annese et al., 1990	[20]	Italy	CC	79	145	3124	3962	Histological	Hospital/voluntary donors
Vioque and Walker, 1991	[21]	Mixed	CC	32	56	104	119	Histological	Hospital
Kokic et al., 1996[c]	[22]	Serbia	CC	1	99	16	84	Histological 62%	Hospital
Guleria et al., 2005	[23]	India	CC	2	6	48	112	NA	Voluntary donors
Zhou and Li, 2005	[24]	China	CC	215	476	354	845	NA	NA
Wolpin et al., 2010[d]	[1]	Mixed	NCC	511	1023	657	926	NA	Cohort members
Risch et al., 2010	[25]	USA	CC	149	224	315	375	Clinical/histological	Population-based
Ben et al., 2010	[26]	China	CC	409	1022	479	970	Histological	Hospital

Abbreviations: Pooled analysis (PA); case-control study (CC); nested case-control study (NCC); and not available (NA).

[a] Pooled analysis of 13 studies representative of all the literature published before 1968.

[b] Number of cases and controls refers to all ABO blood groups.

[c] Risk estimate is for blood type O, Rhesus+.

[d] Pooled analysis from 12 cohorts.

polymorphisms (rs505922) in the ABO gene and pancreatic cancer[3] as well as plasma markers of inflammation (sICAM1, TNF-alpha and E-selectin)[27–29] suggesting a link between chronic inflammatory states and pancreatic cancer, and raising the possibility that blood group antigens may alter the systemic inflammatory response.

Unlike early studies, we did not find an excess of blood group A, and a deficiency of group O, in patients with stomach cancer,[30] which is in agreement with the latest literature: Nijevitch and colleagues[31] found that blood group antigens and helicobacter pylori infection are independently linked to gastroduodenal diseases. More recently, Yei and colleagues[32] found no association between Lewis genotype, mostly found in blood group O, and gastric cancer. El Hajj and colleagues[33] found no differences in the prevalence of O group in patients with gastric adenocarcinoma and in non-donors controls.

However, the lack of statistically significant association for some cancer sites, including endocrine pancreatic tumours, may be due to limited statistical power. In fact our study

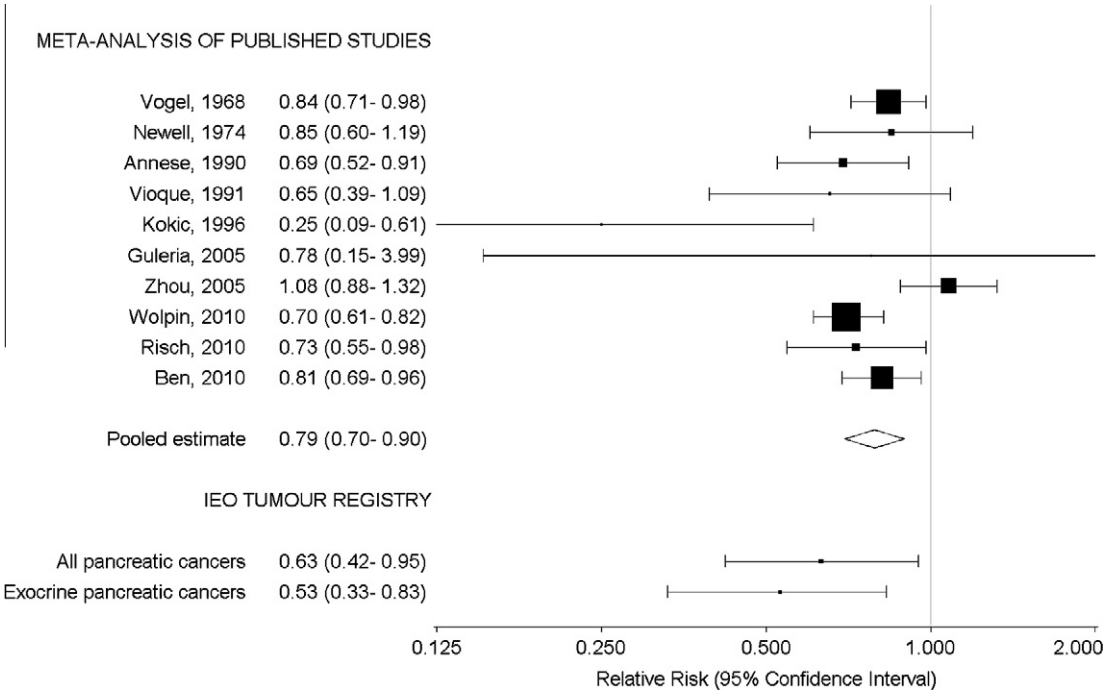

Fig. 2 – Forest plot, summary relative risks and characteristics of studies on pancreatic cancer for patients with O versus non-O blood group.

has enough power (80%) to detect a 20% increase or decrease in the proportion of patients with O blood type only for cancer sites with at least 280 O blood type cases (setting the significance level at 0.05). This issue could represent a possible limitation of our study.

This study confirms and extends the recently reported link between ABO blood group and pancreatic cancer, but restricts the protective effect of O blood type to pancreatic adenocarcinomas. To a large extent, the ABO blood group and cancer link appear to be limited to pancreatic cancer.

Conflict of interest statement

None declared.

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