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Association between ABO Blood Group and Various Types of Cancer: A Case-Control Study in Greek Adults

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Abstract

Background: *The association between ABO blood group and cancer has been identified in many epidemiological researches. The aim of the current research was to investigate the association between ABO blood group and the risk of several types of cancer in a Greek adult population.*

Methods: *A total of 459 individuals who suffered from various types of cancer and 918 non-cancer individuals were enrolled. Blood group data obtained from registration on Identity Patient's Card. The associations between ABO blood group and cancer estimated using multi-variate logistic regression analysis, whereas a multinomial model was carried out to estimate adjusted odds ratios (AORs) for each type of cancer separately.*

Results: *The risk of overall cancer in blood group A and B individuals was significantly higher than that in O and AB groups, (OR=1.96, 95% CI=1.33–2.87, and OR=2.04 95% CI=1.43-2.90, respectively). Compared to blood type O, blood type A was significantly associated with an increased risk of gastric (OR= 2.55, 95% CI= 0.55-4.30), colorectal (OR= 2.06, 95% CI= 0.82-2.58), pancreatic (OR= 2.23, 95% CI= 1.02-2.83), and lung cancer (OR= 2.78, 95% CI= 1.63-5.49), whereas blood type B was significantly associated with an increased risk of esophagus cancer (OR= 1.26, 95% CI= 0.83-1.50), after adjusting for age, gender ,educational and socio-economic status, smoking, and family history of cancer.*

Conclusions: *Those outcomes suggest that ABO blood group is significantly associated with an increased risk of overall cancer. A blood group individual was more likely to develop gastric, esophagus, colorectal, lung, and pancreatic cancer.*

Keywords: *ABO blood group, cancer, risk factors, adults*

Introduction

Cancer is the second leading cause of death worldwide and responsible for 9.6 million deaths in 2018. In Europe cancer causes the second highest number of deaths after Cardiovascular Disease (CVD). Its development is a result of interactions between genetics and environmental factors. Genetic factors include advanced age, male gender, cancer family history and genetic susceptibility. Especially, genetic mutations are responsible for 5-10% of all cancer cases [1]. Environmental etiological and risk factors include cigarette smoking, obesity, previous diseases such as infections with hepatitis B or C (HBV/HCV), Chronic Obstructive Pulmonary Disease, etc., and radiation. However, the mentioned etiological or risk factors can explain only a part of cancer incidence as its clear etiology remains unknown [2-4].

Hereditary types of cancer show, in general, a low prevalence, however inherited biomarkers such as ABO blood group have been associated with the risk of various diseases and types of cancer according to previous and current researches [4].

The ABO blood groups system discovered decades ago [5], is the most immunogenic of all the blood group antigens, its antigens are biomarkers expressed in various types of cells including erythrocytes, mucosa, lung epithelial, and gastrointestinal cells, etc. [6-8]. The ABO gene is an autosomal gene that is located on chromosome 9 at q34.1 to q34.2 region and encodes for a specific glycosyltransferase enzyme that adds a glucose residue to a carbohydrate structure, the H antigen, that is present in the membrane of erythrocytes and other types of endothelial and epithelial cells as already mentioned [9]. Distribution of the 4 different blood groups varies among countries in different geographical, ethnic and socioeconomic groups [10]. Generally, blood group O shows the highest prevalence, while blood group AB shows the lowest. Although the elaborate physiologic function of the ABO blood group antigens remains unknown, no disease results from the lack of ABO blood group antigens expression [9].

An association between ABO blood group and various diseases was proposed 50 years ago [11]. In recent years, several reports have shown that ABO blood group was associated with many diseases and pathological conditions such as coronary heart disease [12], ischemic stroke [13] and various types of cancer [14,15], although the explanation for that relationship is still not understood. Most recent reports based on the finding that such an association was initially suggested through the observation that gastric cancer patients were more likely to have blood type A than control individuals [16], documented a relative link between susceptibility to cancer and ABO blood group or found a relationship between ABO blood group and risk of certain malignancies. Inherited human ABO blood group antigens were associated with various types of malignancies including pancreatic [14,17-38], renal cell [39], skin [15], ovarian [40,41], esophageal [30,42-45], hepatocellular [46-48], colorectal [30,49], oral cavity [50-55], larynx [56], bladder [57], breast [58], gastric [16,30,31,59-67], prostate [68], and lung cancer [30,69-73], but the associations, in general, were inconsistent. For instance, an association between ABO blood group and nasopharyngeal cancer remains controversial as a research by Seow et al. [74], demonstrated the absence of such an association, whereas Turkoz et al. [75] found that ABO blood group was associated with nasopharyngeal cancer susceptibility. Similarly, previous reports investigated the possible association between ABO blood group antigens and risk of lung cancer and proposed a possible association, however, the data on

the role of ABO blood group factor in lung cancer is limited and inconsistent [70,72,73].

Most previous studies were based on self-reporting of blood type which is prone to recall and information biases. In addition, the relatively small sample sizes of most previous studies have limited the opportunity to comprehensively estimate the link between ABO blood group and cancer risks, particularly for rare types of cancers.

No similar retro- or prospective studies of the association between ABO blood group and cancer risk have been carried out in Greece.

The aim of the present retrospective case-control study was to investigate the possible association between ABO blood groups and risk of cancer overall and separately, in several organs in an adult population sample in Greece.

Methods

Study design and study sample

A total of 459 individuals, 200 males and 259 females, who were suffering from various types of cancer and 918 non-cancer individuals, 473 males and 445 females, aged 45-74 years who were selected from two private medical practices enrolled in the study.

The current study was a retrospective case-control study. The case group included patients with several types of cancer and its diagnosis was confirmed according to histolopathological examination of their medical files. The attempt was to choose the controls in such a way they can be the representatives of the population from which the cases were drawn. Thus, cases and controls, were selected from the same city population to avoid or eliminate possible selection biases. In addition, the selection of controls was based on cases' environment, such as friends, colleagues, etc. According to that method, eligible control individuals were selected from those, who were subjected to routine health examinations at the mentioned practices, between 2015 and 2018. Both groups, cases and controls, were matched 2 to 1 with cancer patients for age (± 5 yr), and gender to control potential confounders.

Cancer rates were estimated according to cancer mortality rates in 2012 as no data were available which concerned cancer incidence in Greece [76].

Participants included in the study completed a baseline questionnaire about common risk factors for cancer. Thus, they completed a self-administered questionnaire which concerned information on their medical history, smoking status, socio-economic and educational level, and cancer family history. When at least one first-degree family member was diagnosed with cancer, the family history was considered positive for cancer. The cases who had distant metastases in any one of the organs examined or had a medical history of other malignancies were excluded and included patients with newly diagnosed cancer who were out-patients of the mentioned medical practices in an effort to eliminate potential effects by known and unknown confounders. ABO blood group was confirmed by the medical files of the participants. The distribution of blood groups of controls were similar to the general Greek population.

Variables	Cases (No) (%)	Controls (No) (%)	p-value	Odds Ratio (OR)	95% Confidence Interval (CI)
Gender					
Males	259 (56.4)	473 (51.5)	0.086	0.82	0.66-1.03
Females	200 (43.6)	445 (48.5)			
Age (years)					
45-49	104 (22.7)	277 (30.2)	0.010*	-	-
50-59	164 (35.7)	286 (31.2)			
60-69	157 (34.2)	271 (29.5)			
70+	34 (7.4)	84 (9.2)			
Socio-economic level					
Low	287 (62.5)	539 (58.7)	0.173	1.17	0.93-1.48
High	172(37.5)	379 (41.3)			
Educational level					
Low	242 (5.7)	828 (65.2)	0.000*	0.6	0.48-0.74
High	217 (47.3)	442 (34.8)			
Smoking					
No	148 (32.2)	480 (52.3)	0.000*	0.43	0.34-0.55
Yes	311 (67.8)	438 (47.7)			
Cancer family history					
No	204 (44.4)	476 (51.9)	0.010*	0.74	0.59-0.913
Yes	255(55.6)	442 (48.1)			
ABO blood group					
O	108 (23.5)	244 (26.6)	0.043*	-	-
A	225 (49.0)	391 (42.6)			
B	80 (17.4)	153 (16.7)			
AB	46 (10.0)	130 (14.2)			
*p-value: statistically significant					

Table 1. *Univariate analysis of cases and controls regarding each independent variable examined*

Variables (%)	OC and NPC N (%)	OEC N (%)	GC N (%)	CRC N (%)	HCC N (%)	PC N (%)	LC N (%)
Gender							
Males	7(70.0)	5(71.4)	29(60.4)	38(45.2)	28(53.8)	28(58.3)	124(59.0)
Females	3(30.0)	2(28.6)	19(39.6)	46(54.8)	24(46.2)	20(41.7)	86(41.0)
Age (years)							
45-49	2(20.0)	1(14.3)	8(16.7)	28(33.3)	12(23.1)	8(16.7)	45(21.4)
50-59	3(30.0)	1(14.3)	25(52.1)	38(45.2)	15(28.8)	25(52.1)	57(27.1)
60-69	3(30.0)	3(42.9)	11(22.9)	15(17.9)	17(32.7)	10(20.8)	98(46.7)
70+	2(20.0)	2(28.5)	4(8.3)	3(3.56)	8(15.4)	5(10.4)	10(4.8)
Socio-economic level							
Low	6(60.0)	5(71.4)	32(66.7)	37(44.0)	27(51.9)	12(25.0)	168(80.0)
High	4(40.0)	2(28.6)	16(33,3)	47(56.0)	25(48.1)	36(75.0)	42(20.0)
Educational level							
Low	7(70.0)	4(57.2)	30(62.5)	32(38.1)	31(59.6)	17(35.4)	121(57.6)
High	3(30.0)	3(42.8)	18(37.5)	52(61.9)	21(40.4)	31(64.6)	89(42.4)
Smoking							
No	2(20.0)	1(14.2)	14(29.2)	18(21.4)	17(32.7)	13(27.1)	83(39.5)
Yes	8(80.0)	6(85.7)	34(70.8)	66(78.6)	35(67.3)	35(72.9)	127(60.5)
Cancer family history							
No	3(30.0)	2(28.6)	18(37.5)	35(41.7)	23(44.2)	20(41.7)	103(49.0)
Yes	7(70.0)	5(71.4)	30(62.5)	49(58.3)	29(55.8)	28(58.3)	107(51.0)
ABO blood group							
O	1(10.0)	1(14.2)	9(18.8)	21(25.0)	10(19.2)	13(27.1)	53(25.2)
A	3(30.0)	2(28.6)	21(43.8)	38(45.2)	24(46.1)	18(37.5)	119(56.7)
B	4(40.0)	2(28.6)	10(20.8)	13(15.4)	12(23.1)	12(35.0)	27(12.8)
AB	2(20.0)	2(28.6)	8(16.6)	12(14.4)	6(11.6)	5(10.4)	11(5.3)
Total	10	7	48	84	52	48	210

Table 2. *Distribution of each type of cancer according to independent variables*

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Step 1[a]								
gender	0.226	0.119	3.563	1	0.059	1.253	0.991	1.584
age	0.01	0.062	0.025	1	0.875	1.01	0.894	1.141
smokstat	0.57	0.124	20.974	1	.000*	1.768	1.386	2.257
educlev	0.225	0.132	2.918	1	0.088	1.252	0.967	1.621
socioeclev	-0.138	0.133	1.083	1	0.298	0.871	0.671	1.13
familyhist	0.608	0.122	24.934	1	.000*	1.837	1.447	2.332
O	0.66	0.196	23.651	1	.0	1.936	1.317	2.845
A	0.696	0.181	11.302	3	.001*	2.007	1.407	2.862
B	0.15	0.203	14.782	1	.000*	1.162	0.78	1.729
AB	1.921	0.214	0.544	1	0.461	0.146		
constant			80.96	1	.0			
Step 4[b]								
gender	0.238	0.119	3.999	1	.046*	1.269	1.005	1.602
smokstat	0.54	0.119	20.626	1	.000*	1.716	1.359	2.166
familyhist	0.617	0.12	26.605	1	.000*	1.853	1.466	2.343
O			23.956	3	.0			
A	0.672	0.196	11.772	1	.001*	1.957	1.334	2.873
B	0.711	0.181	15.491	1	.000*	2.035	1.429	2.9
AB	0.173	0.201	0.739	1	0.39	1.189	0.801	1.764
constant	1.869	0.191	95.73	1	0	0.154		

aVariable(s) entered on step 1: gender, age, smokstat, educlev, socioeclev, familyhist, ABO.
bThe reference category is: O blood group.
*p-value: statistically significant

Table 3. *Distribution of each type of cancer according to independent variables*

Cancergen*	Sig.	Exp(B)	95% Confidence Interval for EXP(B)	
			Lower Bound	Upper Bound
ONPCa				
A	0.098	0.936	0.516	1.387
B	0.118	0.673	0.347	1.148
AB	0.214	0.549	0.313	1.133
ESOCa				
A	0.608	1.297	0.485	1.194
B	0.051	1.225	0.825	1.502
AB	0.302	0.872	0.443	1.108
GCa				
A	0.002	2.552	0.546	4.297
B	0.061	1.907	0.774	2.698
AB	0.536	0.857	0.239	1.284
CRCa				
A	0.046	2.059	0.815	2.579
B	0.078	1.308	0.623	1.748
AB	0.119	1.113	0.445	1.274
HCCa				
A	0.103	0.613	0.212	1.176
B	0.066	1.112	0.483	1.629
AB	0.087	0.949	0.49	1.203
PCa				
A	0.304	2.297	1.023	2.826
B	0.077	1.049	0.575	1.424
AB	0.337	0.541	0.285	1.177
LCa				
A	0.022	2.783	1.627	5.486
B	0.178	1.147	0.694	1.298
AB	0.251	0.912	0.542	1.031

ONPCa: Oral and Nasopharyngeal Ca, ESOCa: Esophangeal CA, GCa: Gastric Ca
CRCa: Colorectal Ca, HCCa: Hepatocellular Ca, PCa: Pancreatic Ca, LCa: Lung Ca

Table 4. *Presentation of correlation between ABO blood group and each type cancer according to multinomial logistic regression analysis model*

Statistical analysis

The indices examined coded as dichotomous variables. Male gender, current / former smokers, individuals with higher educational (graduated from University/College) and socio-economic (income/monthly ≥1,000 €) level, cancer family history, and cancer patients were coded as 1, whereas age (45-49, 50-59, 60-69 and 70+) and ABO blood group (O, A, B, AB) were coded as 0, 1,2, and 3 respectively. Each type of cancer was also coded as: 0 for oral and nasopharyngeal (ONPC), 1 for oesophageal (OESC), 2 for gastric (GC), 3 for colorectal (CRC), 4 for hepatocellular (HCC), 5 for pancreatic (PC) and 6 for lung cancer (LC).

The associations between ABO blood group and risk of overall cancer were assessed using uni and multivariate logistic regression analysis. Adjusted Odds Ratios (AOR's) and 95% Confidence Interval (CI) were recorded as well. The independent variables were included in Wald method to assess gradually the variables which showed significant associations with the dependent one. Finally, a multinomial model was carried out to estimate AOR's between ABO blood group and the risk of each type of cancer separately, after adjusting for potential confounders, such as age, gender, smoking status, educational and socio-economic level and family history of cancer. In this analysis, blood type O was used as a reference group.

Statistical analysis was performed using the statistical package of SPSS ver.19.0. A p value less than 5% ($P< 0.05$) was statistically significant.

Results

Cases and controls showed a mean age of 64,5 years (± 3.7). The distribution of cancer patients and controls with ABO group and the univariate analysis is shown in Table1. According to univariate analysis age, educational level, smoking, cancer family history and ABO blood group were found to be significantly associated with overall cancer risk (Table 2).

Table 2 presents the distribution of each cancer type according to the variables examined. Table 3 presents the results after performing of the multivariate regression model. Step1 showed that smoking, cancer family history, A and B blood groups were significantly associated with overall cancer risk. Step 4 showed that the mentioned indices including male gender were significantly associated with overall cancer risk. The same table also shows AOR's and 95% CI.

Table 4 shows the AOR's and 95% CI of ABO blood group categories to each type of cancer. Gastric, colorectal, pancreatic and lung cancer were significantly associated with blood group A, whereas esophageal cancer was significantly associated with blood group B after performance of multinomial regression model and after adjusting for age, gender, educational level and socio-economic status, smoking, and family history of cancer.

Discussion

The association between ABO blood type and many diseases has been investigated for more than 50 years [28,29], however findings to date have little practical value as prevention indices. In the current study, recorded that the risk of GC was higher among individuals with blood type A than those with blood type O. Even though many studies have found a positive association between blood group A and risk of GC, no clear evidence about that association has been suggested [14,61-64].

Another finding was that individuals with blood group O demonstrated a decreased risk of GC [16,59,65-67]. An overview by Zhang et al. examined a total of 36 surveys with 31,783 cancer cases which had investigated the association between ABO blood groups and GC, in Europe and in Asia. Most of those studies found positive and significant associations between blood group A and GC and an inverse association for blood group O compared to non-O groups, whereas 5 studies reported contrary results, but not statistically significant. The pooled OR's showed that individuals with blood type A showed a significantly increased risk of GC compared to those with non-A blood groups, however the heterogeneity among studies could be a possible explanation for those findings [30]. Similar findings recorded by several researchers [31,60]. On the contrary, Iodice et al. [14] failed to confirm the relationship between ABO blood groups and GC.

The biological mechanism by which genetic variants in ABO gene locus influence the risk of GC remains unknown. The ABO gene encodes for a glycosyltransferase, and the A and B alleles encode for proteins which have differences in amino acid sequence and are responsible for the transfer of different carbohydrates into the H antigen which is responsible for the formation of the A or B antigens. On the contrary, the O allele contains a single base deletion and thus, is not able to lead to the formation of the A or B antigens [26]. The mentioned antigens ABO/ABH as has already been said are expressed on the erythrocytes surface and many other tissues [77], are crucial intercellular adhesion and membrane signaling mediators, and are involved in the malignant cells progression and dissemination [78]. Those antigens are also recognized by the host immune system and may affect immunosurveillance for malignant cells [24,78]. Another explanation for the association between ABO blood type and GC risk could be that is a result through an effect on the differences among ABO alleles in atrophic gastritis prevalence and H. Pylori infection, as both conditions are risk factors for GC development [67].

A potential explanation for the increased incidence of GC in blood group A individuals could be the fact that individuals with blood group A were more susceptible to pernicious anemia, compared with non-A blood group ones [79], as individuals who suffer from pernicious anemia are more prone to GC [80].

The results also showed an increased risk of ESOC for individuals with blood group B, whereas the significance level was marginal ($p= 0.051$). Previous studies confirm the result of the present study. A review by Zhang et al. [30] showed that in 6 studies blood type B was associated with an increased rate of ESOC but only one of the surveys examined was statistically significant. The pooled analysis revealed that ESOC risk for blood group B was significantly higher than non-B groups, and that ESOC risk for blood group O was significantly lower than non-O groups. Similar observations have been found in previous studies, whereas it has also been reported that blood group B was associated with ESO squamous cell carcinoma and blood group O was associated with ESO adenocarcinoma [42,44,45].

The current study showed that individuals with blood group A had a significantly increased risk of CRC compared to those with non-A blood group, findings that agreed with those from a previous study [49]. A decreased risk of CRC for individuals with blood group O was recorded in a systematic review with 6,931 cancer cases, however a high heterogeneity was found across 7 case-control and 1 cohort study which totally examined [30].

On the contrary, in another prospective cohort study was not found any statistically significant association [81], whereas other similar previous studies found no association as well [69,82,83]. A possible explanation for the association examined could be attributed to alterations on the ABH blood group antigens which can change the cell-cell and cell-extracellular matrix interactions and those abnormalities can lead to tumor development. In addition, alteration of ABO/Lewis antigen has been found to be related to malignant transformation in some tumors [84]. An increased risk of LC for individuals with blood group A was also recorded in the current study. In a similar multicenter retrospective study reported that ABO blood type was associated with LC risk and non-O blood type was associated with an increased risk of LC, whereas blood group O was associated with a 14% risk reduction of LC [70]. A significant excess risk was found among individuals with blood group A in another study [71]. In contrary to previous findings two recent and one previous study recorded no association between ABO blood groups and risk of LC [69,72,73]. The relationship between LC and blood groups was assessed in one review study with 1,561 cancer cases. All the studies showed a protective effect of LC for blood group B compared to non-B groups, but not statistically significant. However, statistically significant heterogeneity was observed among the studies reviewed [30].

The possible association between ABO blood group and PC risk has been investigating for decades, however that association has not been consistently recorded. Retrospective case-control reports which carried out in the 1960s and '70s found an increased risk of PC in individuals with blood group A [28,29,32], compared to those with blood group B or O. A significant association was observed in the current study between blood type A and the risk of PC. Recent studies confirm that finding [14,19,22,33,34]. A meta-analysis by Zhang et al. [30] with 8,068 cases showed that only one study recorded an inverse association for blood group A compared to non-A groups but was not statistically significant. The pooled OR's showed an increased risk for blood group A on PC risk and a protected effect for blood group O on PC risk; however, a median heterogeneity was present. An increased PC risk for individuals with blood group A when compared with O individuals found in a recent large study with 1.6 million blood donors who were followed over an average of 17 years [23].

However, similar studies recorded different associations. A previous case-control study found an increased rate of blood group B among PC patients compared to two different randomly selected groups from the same hospital [85], and more recent studies confirmed that finding [24,25,31]. Results from two large, independent prospective cohorts of Caucasians suggested that compared with blood group O individuals, those with non-O blood types (A, AB or B) were more likely to develop PC [19,26,35].

Non-O blood types were associated with an elevated risk of PC [31]. It has been demonstrated that blood group O individuals have a lower risk of PC [86], whereas for the other blood types, the data is not always consistent as has already been mentioned.

Two large case-control studies on Chinese patients showed that blood group O was associated with a lower incidence of PC, compared with blood groups A and AB [17,37], whereas another study showed that blood group AB is protective against PC risk [38].

One hypothesis proposes that the difference in ABO antigens in gastric mucins affects the properties of H. Pylori binding and explains the difference in PC risk among ABO blood types [38].

A recent study recorded that only the A1 allele was associated with significantly higher risk for pancreatic ductal adenocarcinoma after comparison ABO allele frequencies in PC patients and blood donors [86].

Chronic inflammation of pancreas is a predisposing factor for pancreatic tumorigenesis. PC affects a strong desmoplastic

reaction that supports tumor invasion, growth and metastases as is responsible for the presence of inflammatory mediators in blood circulation [87,88]. Recent and previous reports have found a relation between chronic inflammation and cancer, including pancreatic ductal carcinoma [88,89] and as has already mentioned the ABO blood antigens may affect the systemic inflammatory reaction. To be more specific, recent genome-wide association studies (GWAS) and similar designed studies recorded an association between ABO gene locus and PC risk [24-26,90] and suggested that ABO blood group antigens may affect the systemic inflammatory status [91,92] and that single nucleotide polymorphisms at the ABO locus were associated with TNF-α [92] and soluble intercellular adhesion molecule-1(sICAM-1) [91], which are known inflammatory biomarkers. TNF-α is a pro-inflammatory cytokine which regulates pancreatic ductal cell apoptosis [87], whereas plasma levels of sICAM-1 are associated with the risk of diabetes mellitus development [93], which increases the susceptibility for PC. Thus, it is

possible that ABO blood group antigens may alter the systemic inflammatory conditions and influence the risk of PC development. These reports suggest the possibility that ABO blood group may correlate with the systemic inflammatory state, thereby influencing the risk of PC [24].

The ABO antigens are expressed not only on the erythrocytes surface but are highly expressed on the surface of epithelial cells of the gastrointestinal, bronchopulmonary, and urogenital tracts as has already said [78]. Studies have shown the deletion and the novel expression of A, B, and H antigens on the surface of PC cells compared with surrounding normal ductal cells [8,37,94,95], suggesting that alterations in glycosyl-transferase specificity may occur during pancreatic tumorigenesis. Glycosyl-transferase specificity has wide implications, beyond defining ABO blood type [96].

ABO blood antigens are important mediators of intercellular adhesion and membrane signaling, two processes integral to malignant progression and dissemination, whereas antigens are recognized by the host immune response and may have a role in facilitating immune surveillance for malignant cells [97]. Alterations in the host inflammatory state due to ABO blood group antigens may provide a further mechanism to explain an association between blood type and PC risk.

No association was observed between ABO blood group and the risk of HCC. However, a small number of previous studies recorded associations between the ABO blood group and liver diseases, including HCC [47,48]. A case-control study in China which examined 1,105 HCC patients was first reported the possible association between HCC and blood group A [46]. In recent studies in Taiwan and Korea, higher risk for HCC also observed in the presence of A antigen [71,98], whereas in another study found that men with blood type A or B showed a significantly higher HCC risk compared with men with blood type O which was independent of the known HC risk factors [46].

In regard to the relation between ABO blood group and the risk of HCC various explanations have been suggested. ABO blood group is associated with various serum biomarkers which are involved in HCC development. Such biomarkers are the inflammatory associated cytokines TNF-α, EGF, sICAM-1, P-selectin and E-selectin [91,92,99-101]. The Epidermal Growth Factor Receptor (EGFR) is a crucial receptor and is implicated in inflammation and in HCC [102], whereas its gene polymorphisms have been suggested to be associated with HCC risk [103,104]. The interaction between EGF and its ligand differs between blood groups A and O, and loss or gain of the A antigen expression may affect cell signaling pathways and cellular growth [100]. ABO antigens act as receptors or ligands for bacteria and immunologically enzymes [105] that are involved in malignant progression and dissemination [78]. Thus, the abnormal ABO blood antigens expression in liver cells tissue might be associated with HC carcinogenesis. In healthy liver cells the ABO blood antigens A, B, and H, are not expressed on their surfaces. However, increased ABH expression or neo-expression has been found in HCC cells [106].

The non-O blood group is an independent risk factor for the progression of liver fibrosis in HCV infection [107], whereas individuals with blood group A show more liver dysfunction and earlier appearance of liver cirrhosis compared to individuals with blood group A [46]. Those observations suggest an association between ABO blood groups and liver inflammation and fibrosis progression in patients with CHB which can lead to HC carcinogenesis.

Based on the current study, no association was recorded between the ABO blood group and the risk of oral/nasopharyngeal cancer, findings that agreed with those of recent GWAS on NPC [108-111].

However, Akhtar et al. showed that individuals with blood group B and those older than 50 years of age had increased risk of developing oral cancer [51], whereas in another report in Iranian population was found that individuals with blood group B were at a greater risk to develop oral cancer [52]. Similarly, Sharma et al. also recorded that in cancer of the buccal mucosa blood group B showed the highest frequency, however it was not statistically significant [112]. On the contrary, individuals with blood group A had a higher risk of developing oral cancer followed by B blood group according to another report [53], whereas it has also been shown that individuals with blood group A were more susceptible to the development of oral cancer [54,55]. Turkoz et al. confirmed that ABO blood group is associated with NPC susceptibility, as were observed that blood group A increases the cancer risk, whereas blood group O has a protective effect [75]. A review which performed by Zhang et al. with 1,872 cases showed that the risk of NPC for blood group A was significantly higher than non-A groups, and for blood group O the risk was significantly lower than non-O groups, whereas there was no evidence of heterogeneity across studies [30].

Different findings were recorded by Sheng et al. who found that blood types A or AB is associated with an increased risk of NPC [113].

Those differences could be attributed to diversity in sample size, study design and races of participants, whereas that association between ABO blood groups and the risk of cancer may vary among different geographic localizations and races or ethnicities [15].

Previous investigations indicated that ABO antigens mediate microbial infections, including H. Pylori [22,114] and Norwalk virus [115]. Thus, it is possible that ABO status may also interact with EBV and influence NP carcinogenesis. However, the lack of information on EBV infections sets limits the current study, which may display a bias in the analysis.

The current study has certain limitations that should be considered during the interpretation of the results. Case-control studies do not have the reliability of the prospective ones, whereas selection, recall, random, referral biases and the effect of known and unknown confounders are likely higher and could lead to biased secondary associations regarding the variables examined. In addition, possible confounding factors which are related with to increased risk of various types cancer were not included.

The results for overall cancer may be conducted by the cancer sites with more studies included, as the number of studies on different cancer sites included in the current study varied largely. Significant heterogeneity was observed across studies, which may be caused by sample sizes, participants' characteristics, study design, and confounding factors.

A potential limitation of those studies which are based on questionnaires is that the individuals either could not respond or could give no reliable responses or could over- or under-estimate their potential medical diseases or disorders. Another limitation

relates to the selection of controls group, which may attitude a challenge for ABO phenotype and other features with an ABO distribution which varies by geography and ethnicity.

Although the current study had a relatively large sample size in general, the numbers of individuals in some subgroups were small. In addition, the data analyses based on cancer mortality as data which concerned the cancer incidence in Greece were not available.

Some strengths of the current study were that it was a matched case-control study and used randomly selected population-based controls. Because the control population was selected from non-cancer individuals derived from cases environment, it is reasonable to assume that these individuals represented the same base population as that from which the cases were selected, warranting internal validity. Thus, the distributions of demographic and epidemiologic factors, including age, gender, and smoking, differed between cases and controls. Younger individuals than 45 years were excluded to minimize potential bias. Residual confounding may not affect the main results because all potential confounders, such as cancer family history or smoking, could be adjusted for in this study. The respective ABO genotype frequencies of O, A, B, and AB in controls, were consistent with those of previous population-based controls and according to the general population frequencies. Finally, the consistency of blood group data was confirmed with the information registered on the Patient's Identity Card.

Potential limitations which concern each type of cancer are also important. HCC could be attributed to chronic hepatitis B/C, however the data are insufficient for our statistical analysis. The number of O/NP and ESO cancer patients in the current study was insufficient for analysis. A potential source of bias was the medical status of the controls. Lack of consideration of chronic pancreatitis as a potential cause of PC in the analysis could also be a limitation in the present study. In addition, the current study did not examine the possible susceptibility to PC in diabetic patients. Finally, some of the known risk factors of cancer were examined and not specific as drinking consumption, previous infection by EBV, exposure to atmosphere pollutants, nutrition habits, etc.

A retrospective design of a study cannot avoid recall or selection bias, thus prospective cohort studies with larger number of patients are necessary to define the mechanisms by which ABO blood type may influence cancer risk and may clarify the role of blood groups in the population examined. Another reason is the relatively limited number of cases which also indicates that those findings need replication in a larger study.

In conclusion in that study, it was found an association between A and B blood groups and the risk of various types of cancer.

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