Original article

Blood group phenotypes associated with risk of gastric cancer: a case-control study

Nasser Alzerwi[1], Bandar Idrees[2],

1. Department of Surgery, College of Medicine, Majmaah University, Ministry of Education, Al Majmaah City, 11952, P. O. Box 66, Riyadh Region, Kingdom of Saudi Arabia.
2. Consultant of Surgical Oncology, Gastrointestinal, Biliopancreatic, and Minimally Invasive Surgery at Department of Surgery, Prince Sultan Military Medical City in Riyadh, Clinical Assistant Professor of Surgery at Al-Faisal University, College of Medicine, Department of Surgery, Riyadh city

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Correspondence author:
Nasser Alzerwi Department of Surgery, College of Medicine, Majmaah University, Ministry of Education, Al Majmaah City, 11952, P. O. Box 66, Riyadh Region, Kingdom of Saudi Arabia. Email n.alzerwi@mu.edu.sa

Abstract

Background & Aims:
The association of the ABO blood groups with gastric cancer is controversial and was examined in this study.

Methods:
We conducted a case-control study of 2145 cases of gastric cancer and 2472 controls of Korean ethnicity to determine the risk of gastric cancer for each blood group phenotype using multivariable logistic regression models.

Results:
Patient ages were 33.3 (SD = 9.76) years in controls compared to 59.5 (SD = 11.91) years in cases. The percentages of males and females were similar among cases and controls. The crude OR revealed phenotype O as a protective factor 0.63 (CI: 0.56–0.72) (P < 0.0001) compared to phenotype A 1.30 (CI: 1.15–1.47) (P < 0.0001) and AB 1.29 (CI: 1.07–1.57) (P < 0.01), which were risk factors for gastric cancer, and phenotype B 1.09 (CI: 0.94–1.24) (P = 0.27)

الملخص

الخلفية و الأهداف:
إن وجود علاقة إرتباطية بين فصائل الدم المختلفة و قابلية الإصابة بسرطان المعدة، لطالما كانت محل البحث و الدراسة، و كانت النتائج متناقضة و محل جدل، و الهدف من هذه الدراسة هو تقصي هذه العلاقة.

طريقة البحث:
قمنا بعمل دراسة حالات وشواهد على ٢١٤٥ حالة سرطان معدة من العرق الكوري، و مقارنتها ب ٢٤٧٤ شاهد من العرقية الكورية ، بإستخدام الإنحدار اللوجيستي المتعدد، للتحقق من وجود علاقة إرتباطية بين الحالات والشواهد و مختلف فصائل الدم.

النتائج:
كان متوسط أعمار الحالات ٣٣.٣ (إنحراف معياري =٩.٧٦)، مقارنة ب ٥٩.٩ (١١.٩١) عند الشواهد، نسب تمثيل الذكور و الإناث بين الشواهد و الحالات كانت متقاربة، نسبة الإحتمالات المبسطة كشفت أن فصيلة الدم O هي عامل وقاية من سرطان المعدة ٠.٦٣ (فاصل ثقة: ٠.٥٦ – ٠.٧٢) (قيمة إحتمالية: ٠٠٠١.) ، مقارنة ب فصيلتي الدم أ ١.٣٠ (فاصل ثقة: ١.١٥ – ١.٤٧) (قيمة إحتمالية: ٠٠٠١.) ، و أ-ب ١.٢٩ (فاصل ثقة: ١.٠٧ – ١.٥٧) (قيمة إحتمالية: ٠٠١.)، كعاملي خطر للإصابة بسرطان المعدة، مقارنة بفصيلة ب ١.٠٩ (فاصل ثقة: ١.٢٤ – ١.٩٤)

which was neither protective nor a risk factor. The adjusted OR taking patient characteristics into account and using blood group phenotype O as a reference baseline risk showed that phenotype A (1.21; CI: 1.14–1.39) (P = 0.012) and phenotype AB (1.17; CI: 1.08-1.26) (P = 0.038) conferred an increased risk for gastric cancer compared to phenotype B (0.97; CI: 0.84–1.04) (P = 0.63), which was not associated with gastric cancer risk.

Conclusions:
We revealed an association of blood group phenotypes A and AB with gastric cancer risk, emphasizing the need to further study the underlying molecular mechanism of this association with gastric cancer.

Keywords:
ABO blood group phenotype, Gastric carcinoma, Case-control study

(قيمة إحتمالية: ٠.٢٧)، كعامل محايد. بينما كشف الإنحدار اللوجيستي المتعدد ، آخذا بالإعتبار عوامل الإلتباس، و متخذا فصيلة الدم O كمرجع، عن نسبة إحتمالات معدلة لفصيلتي أ ١.٢١ (١.١٤- ١.٣٩) (قيمة إحتمالية: ٠.٠١٢) ، و أ-ب ١.١٧ (١.٠٨ – ١.٢٦) (قيمة إحتمالية: ٠.٠٣٨) ، مقارنة بفصيلة ب ٠،٩٧ (٠،٨٤ – ١،٠٤) (قيمة إحتمالية: ٠.٦٣).

الخلاصة:
إن قبيلتي الدم أ و أ-ب ، لهما علاقة إرتباطية يخطر الإصابة بسرطان المعدة، ذات دلالة و أهمية إحصائية و سريرية ، تستدعي إجراء دراسات أعمق لمحاولة تحديد وفهم طبيعة هذه العلاقة الإرتباطية على المستوى الجزيئي في آلية التسرطن لسرطان المعدة.

Background

ABO blood group antigens are extracellular complex carbohydrate antigens expressed not only on red blood cells but also on various other cell types, including epithelial, vascular endothelial, and sensorineural cells and platelets [1,2].These antigens were discovered in 1900 by Karl Landsteiner and provided insight into the human genetic make-up before the era of human genomic analysis. The blood group antigens were found to be associated with multiple human diseases [3], including hematological and transfusional diseases as well as cardiovascular and oncological diseases [4, 5, 6]. Whether this association is a marker of an underlying oncogene or if these antigens play a direct role in carcinogenesis is not fully understood; however, multiple biological mechanisms have been proposed for ABO antigens in human carcinogenesis [3, 7] .The association of ABO antigens with gastric epithelial diseases is well-established, including peptic ulcer disease, Helicobacter pylori infection, pernicious anemia and atrophic gastritis, stomal ulcers, and gastric cancer [7-14]. The first reported association between a disease and genetic indicator was the association between blood group A and gastric cancer (GC) in 1953 [15]. Since then, this associ-

ation has been extensively investigated, but the studies have shown controversial results [10,16, 17].

The most popular theory regarding the mechanism through which antigen A is involved in increasing the risk of GC is that this antigen reduces the antigenicity of GCs by inducing immunological tolerance and evasion of immunological surveillance, as GC cells produce an antigen that is immunologically related to antigen A. This also explains the protective effect of blood group O, which enhances tumor antigenicity and prevents neoplastic growth and dissemination by enhancing immuno-surveillance [3, 18]. GC is the fourth most common malignancy and second leading cause of death from cancer internationally [19, 20] according to the World Health Organization, particularly in East Asia, such as Mongolia, Japan, and Korea; Korea shows the highest incidence of GC in both sexes worldwide [21, 22]. It is also the most common cause of death in western Asian countries such as Iran, Turkmenistan, and Kyrgyzstan [22], with risk variation between the highest-risk and lowest risk populations reaching 15–20-fold [23]. Survival rates also vary widely, with the highest survival rate in Japan (90%) compared to 10–30% in Europe [23].

Non-modifiable risk factors such as age (12.8–19.8 per 100,000 for those above 60 years old, compared to 2.0–2.6 per 100,000 in those below 60 years old) [24], sex (2-fold more common in males than in females) [22], and family history (3-fold increase with a positive family history of first-degree relatives with GC [25]; however, GC also exhibits a strong modifiable risk factor element as shown in emigration studies, with significant reduction in risk in 3rd-generation Japanese immigrants to the USA [26], and a reduced risk of GC with eradication of H. pylori [27]. Thus, epidemiological studies of modifiable and non-modifiable risk factors and their interactions are needed for the prevention, early detection, and identification of new targets for biological therapy [10, 28, 29]. This study was conducted to explore the association between ABO antigens and GC in an ethnically homogenous group of Korean subjects. The results were compared to those of similar studies in the literature.

Methods

Study Design

This was a retrospective case control study.

Participants

Cases were histopathologically confirmed as GC with no previous history of peptic ulcer disease or seropositivity or treatment for H. pylori (n = 2145) from Saint Mary Catholic University Hospital, Seoul, Re-

public of Korea, and controls were cancer-free blood donors (n = 2472) from the blood bank at the same hospital with no previous history of peptic ulcer disease or seropositivity or treatment for H. pylori between March 2010 and December 2014. All participants were of Korean ethnicity and unrelated (through random sampling technique). Blood groups were identified phenotypically using standard serological methods.

Written informed consent was obtained from all participants. The Institutional Review Board approved the research protocols at the hospital. The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Statistical analysis

Analyses were conducted using SPSS 26 software (SPSS, Inc., Chicago, IL, USA). The differences in characteristics between cases and controls were determined using descriptive statistics. The normal distribution and homogeneity of variance assumptions were checked using Kolmogorov-Smirnov and Shapiro-Wilk normality tests and were violated for all variables, and thus nonparametric tests were used to compare different categories of variables. For continuous variables, Mann-Whitney U test (also known as Wilcoxon rank-sum test) was used to detect differences in characteristics between cases and controls. Kruskal-Wallis tests were used for continuous variables with more than two categories. Games-Howell post-hoc test was conducted when there was a significant difference between categories. For categorical variables, we performed Pearson's $\chi 2$-test. The ABO-GC risk association was assessed using multivariable unconditional logistic regression models adjusting for age, sex, body mass index (BMI), smoking status, drinking status, and family history to determine the adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Participants with the ABO phenotype O were considered as having a baseline risk. Two-tailed P values < 0.05 were considered as statistically significant. The sample size was calculated to be 1,067 patients in each arm to achieve 90% power to detect a 3% difference in in outcome variation.

Results

General participants characteristics

Participants' characteristics are summarized in Tables 1, 2, and 3. There were no significant ($P > 0.05$) differences between cases and controls in age, sex, BMI, smoking status, drinking status, or family history of GC. Only comorbidity was significantly different between cases and

controls (Table 1). There were 2472 controls and 2145 cases; Tables 2 and 3 show the subgroup distribution of demographics (age, sex, family history, BMI, and comorbidity status) and lifestyle habits (smoking status and drinking status) among the blood groups between controls and cases, and tumor stage (TNM staging, early vs. advanced), and type of operation (surgical access and extent of gastrectomy) between blood groups among cases.

GC risk by blood group phenotypes

The crude OR was calculated and compared to the adjusted OR for these variables using multivariable logistic regression models (Table 4). The distributions of blood groups O, A, B, and AB in the controls were 37.1%, 33.1%, 21.0%, and 8.94% and in cases were 27.18%, 39.3%, 22.24%, and 11.28%, respectively. The crude OR revealed that phenotype O was a protective factor for GC (0.63; CI: 0.56–0.72) ($P < 0.0001$) compared to phenotype A (1.30; CI: 1.15–1.47) ($P < 0.0001$) and AB (1.29; 1.07–1.57) ($P < 0.01$), which were risk factors for GC. The crude OR for phenotype B was 1.09 (CI: 0.94–1.24) ($P = 0.27$), revealing that it is not protective nor risk for GC in this study. The adjusted OR for age, sex, family history of GC, BMI, comorbidity status, smoking status, and drinking status using multivariable logistic regression models, using phenotype O as a reference baseline risk of 1.00, revealed an adjusted OR for phenotype A of 1.21 (CI: 1.14–1.39) ($P = 0.012$), AB of 1.17 (CI: 1.08–1.26) ($P = 0.038$), and B of 0.97 (CI: 0.84–1.04) ($P = 0.63$), indicating a confounding effect for other risk factors on the crude OR.

Table 1. Comparison of participants' characteristics between controls and cases.

Variable		Control	Gastric Cancer Cases
No		**2472**	**2145**
Age	Mean (SD)	33.3 (9.76)	59.5 (11.91)
	≤65 (%)	1755 (71.0%)	1357 (63.26%)
	>65 (%)	717 (29.0%)	788 (36.74%)
Gender	F n (%)	936 (37.86 %)	714 (33.29%)
	M n (%)	1536 (62.14%)	1431 (66.71%)
Smoking Status	Smoker n (%)	1049 (42.44%)	929 (43.33%)
	None-smoker n (%)	1423 (57.56%)	1216 (56.67%)
Drinking Status	Drinker n (%)	1389 (56.19%)	882 (41.12%)
	Non-drinker n (%)	1083 (43.81%)	1263 (58.88%)

[a] Comorbidity	Yes n (%)		112 (4.53%)		2082 (97.06%)	
	No n (%)		2360 (95.47%)		63 (2.94%)	
Family history of GC	Yes n (%)		746 (30.18%)		609 (28.39%)	
	No n (%)		1726 (69.82%)		1536 (71.61%)	
BMI Mean (SD)	Mean (SD)		20.83 (2.14)		23.45 (3.36)	
TNM Stage	I n (%)		-		1637 (63.73%)	
	II n (%)				301 (14.03%)	
	III n (%)				330 (15.38%)	
	IV n (%)				147 (6.86%)	
Early Vs Advanced	EGC n (%)		-		1329 (61.96%)	
	AGC n (%)				816 (38.04%)	
Surgical Access	Laparoscopic n (%)		-		1009 (47.04%)	
	Open n (%)				1136 (52.96%)	
Gastrectomy Extent	TG n (%)		-		550 (25.64%)	
	STG n (%)				1430 (66.67%)	
	Other n (%)				165 (7.7%)	
ABO-Rh n (%)	A	Rh+	818 (33.1%)	816 (99.76%)	843 (39.3%)	842 (99.88%)
		Rh-		2 (0.24%)		1 (0.12%)
	B	Rh+	517 (21.0%)	514 (99.42%)	477 (22.24%)	476 (99.79%)
		Rh-		3 (0.58%)		1 (0.21%)
	O	Rh+	916 (37.1%)	915 (99.89%)	583 (27.18%)	580 (99.50%)
		Rh-		1 (0.11%)		3 (0.50%)
	AB	Rh+	221 (8.94%)	220 (99.5%)	242 (11.28%)	241 (99.58%)
		Rh-		1 (0.5%)		1 (0.42%)

SD: standard deviation, n: number of participants, F: female, M: male, P: probability value, BMI: body mass index, ABO: blood groups, Rh: rhesus factor, GC: gastric cancer, EGC: early gastric cancer, AGC: advanced gastric cancer, TNM: T for tumor .depth, N for nodal status, M for metastases, comorbidity: DM, HTN, IHD, Hyperlipidemia, a: P = 0.034

Table 2. Comparison of participants' characteristics by ABO-Rh between controls and cases.

Variable		Control				Gastric Cancer Cases			
No		2472				2145			
		A	B	O	AB	A	B	O	AB
ABO n (%)		818 (33.1%)	517 (21.0%)	916 (37.1%)	221 (8.94%)	843 (39.30%)	477 (22.24%)	583 (27.18%)	242 (11.28%)
Rh	Rh+ n (%)	816 (99.76%)	514 (99.42%)	915 (99.89%)	220 (99.5%)	842 (99.88%)	476 (99.79%)	580 (99.50%)	241 (99.58%)
	Rh- n (%)	2 (0.24%)	3 (0.58%)	1 (0.11%)	1 (0.5%)	1 (0.12%)	1 (0.21%)	3 (0.50%)	1 (0.42%)
Age	Mean (SD)	28.6 (9.03)	31.4 (8.94)	33.1 (8.57)	40.2 (8.79)	58.88 (6.38)	59.52 (5.97)	60.55 (4.86)	59.07 (5.73)
	≤65 (%)	671 (82.03%)	368 (71.18%)	599 (65.4%)	117 (52.94%)	561 (66.55%)	299 (62.68%)	356 (61.06%)	141 (58.26%)
	>65 (%)	147 (17.97%)	149 (28.82%)	317 (34.6%)	104 (47.06%)	282 (33.45%)	178 (37.32%)	227 (38.93%)	101 (41.74%)
Gender	F n (%)	314 (38.4%)	211 (40.8%)	332 (36.2%)	79 (35.7%)	291 (34.52%)	161 (33.75%)	182 (31.22%)	80 (33.06%)
	M n (%)	504 (61.6%)	306 (59.2%)	584 (63.8%)	142 (64.3%)	552 (65.48%)	316 (66.25%)	401 (68.78%)	162 (66.94%)
Smoking Status	Smoker n (%)	386 (47.2%)	170 (32.9%)	415 (45.3%)	78 (35.3%)	351 (41.64%)	199 (41.7%)	275 (47.17%)	104 (43.0%)
	None-smoker n (%)	432 (52.8%)	347 (67.1%)	501 (54.7%)	143 (64.7%)	492 (58.36%)	278 (58.3%)	308 (52.83%)	138 (57.0%)
Drinking Status	Drinker n (%)	422 (51.59%)	335 (64.8%)	487 (53.17%)	145 (65.61%)	349 (41.4%)	188 (39.41%)	251 (43.05%)	94 (38.84%)
	Non-drinker n (%)	396 (48.41%)	182 (35.2%)	429 (46.83%)	76 (34.39%)	949 (58.60%)	289 (60.59%)	332 (56.95%)	148 (61.16%)
[a] Comorbidity	Yes n (%)	29 (3.54%)	23 (4.45%)	57 (6.2%)	3 (1.36%)	822 (97.51%)	461 (96.65%)	559 (95.88%)	237 (97.90%)
	No n (%)	789 (96.46%)	494 (95.55%)	859 (93.8%)	218 (98.64%)	21 (2.49%)	16 (3.35%)	24 (4.12%)	5 (2.10%)
Family history of GC	Yes n (%)	267 (32.64%)	160 (30.9%)	232 (25.33%)	87 (39.37%)	249 (29.54%)	132 (27.67%)	160 (27.44%)	68 (28.10%)
	No n (%)	551 (67.36%)	357 (69.1%)	684 (74.67%)	134 (60.63%)	594 (70.46%)	345 (72.33%)	423 (72.56%)	174 (71.90%)
BMI Mean (SD)	Mean (SD)	19.7 (1.37)	20.1 (1.49)	18.9 (0.86)	24.6 (2.26)	23.41 (2.89)	23.61 (3.04)	23.38 (2.91)	23.59 (3.13)
TNM Stage	I n (%)	-				543 (64.41%)	304 (63.73%)	376 (64.50%)	144 (59.50%)
	II n (%)					135 (16.01%)	53 (11.11%)	79 (13.55%)	34 (14.05%)
	III n (%)					112 (13.29%)	88 (18.45%)	87 (14.92%)	43 (17.77%)
	IV n (%)					53 (6.29%)	32 (6.71%)	41 (7.03%)	21 (8.68%)
Early Vs Advanced	EGC n (%)	-				537 (63.70%)	292 (61.22%)	361 (61.92%)	139 (57.44%)
	AGC n (%)					306 (36.30%)	185 (38.78%)	222 (38.08%)	103 (42.56%)
Surgical Access	Laparoscopic n (%)	-				387 (45.90%)	228 (47.80%)	278 (47.68%)	116 (47.90%)
	Open n (%)					456 (54.10%)	249 (52.20%)	305 (52.32%)	126 (52.10%)

Gastrectomy Extent	TG n (%)	-	202 (23.96%)	119 (24.95%)	166 (28.47%)	63 (26.03%)
	STG n (%)		567 (67.26%)	332 (69.60%)	369 (63.3%)	162 (66.94%)
	Other n (%)		74 (8.78%)	26 (5.50%)	48 (8.23%)	17 (7.25%)

SD: standard deviation, n: number of participants, F: female, M: male, P: probability value, BMI: body mass index, ABO: blood groups, Rh: rhesus factor, GC: gastric cancer, EGC: early gastric cancer, AGC: advanced gastric cancer, TNM: T for tumor depth, N for nodal status, M for metastases, comorbidity: DM, HTN, IHD, Hyperlipidemia, a: P = .034 between cases .and controls

.Table 3. Association of ABO with gastric cancer

ABO type	Controlsn (%) 2472	Gastric Cancer Cases n (%) 2145	OR (95% CI)			
			Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
O	916 (37.1%)	583 (27.18%)	0.6340 (0.5593–0.7187)	<0.0001	1.00 (reference)	-
A	818 (33.1%)	843 (39.3%)	1.3021 (1.1542–1.4689)	<0.0001	1.21 (1.14–1.39)	0.012
B	517 (21.0%)	477 (22.24%)	1.0914 (0.9396–1.2446)	0.27	0.97 (0.84–1.04)	0.63
AB	221 (8.94%)	242 (11.28%)	1.2953 (1.0687–1.5699)	<0.01	1.17 (1.08–1.26)	0.038

n: number of participants, P: probability value, ABO: blood groups, CI: confidence interval, OR: Odds ratio, a: multivariable .adjustment by age, gender, smoking status, drinking status, BMI category, family history of gastric cancer, and comorbidity

Discussion

The ABO blood group distribution exhibits its significant variation among different ethnic groups and geographical territories [16,30]; thus, we evaluated cases and controls from the same ethnically homogenous Korean population to explore the qualitative and quantitative nature of the association between ABO blood groups and GC. Although standard serological phenotypical determination of blood groups may lead to different predictions and results in contrast to genotype determination, these differenc-

es are negligible in ethnically homogenous populations, as the reported discordance rate between phenotypical and genotypical grouping is 0.12% in Korea and 0.18% in Japan [20-33]. The association between ABO blood groups and gastric carcinoma has been extensively investigated. Although the results are conflicting [10, 16, 17], group A is recognized as an established risk factor for GC [10, 15, 34-36], which was confirmed in the present study (crude and adjusted OR) (Table 4), as well as in a recent large scale prospective study using standard serological ABO blood grouping [37].

Our study also confirmed the protective effect of group O against GC (crude OR) (Table 4), which has been demonstrated in multiple previous studies [3, 18], and is a protective factor against certain types of skin cancer [36] and pancreatic exocrine carcinoma [17, 39, 40]; however, group O has been shown to be a risk factor for benign gastric epithelial diseases (e.g., gastric peptic ulcer disease, H. pylori infection, and stomal ulcers) [8, 9, 11, 37]. This study is also consistent with previous studies showing that group B is neither a risk nor a protective factor for GC [33] (Table 4); however, group B is a risk factor for ovarian carcinoma [41], and vulvar cancer[42], and group O although protective factor for ovarian and vulvar cancer[42], is associated with increased risk of relapse of these cancers[42]. The most important finding of our study is that group AB is also a risk factor for GC (Table 4), which has been observed in few other studies, particularly in populations of Asian descent [43]; however, this meta-analysis showed that the risk factor effect of the AB group was maintained in the subgroup suffering from a high prevalence of H. pylori infection compared to that with a low prevalence of H. pylori infection, which may be a significant confounding factor [43] given that the AB group is considered a protective factor against H. pylori infection [11]. Thus, we found that the AB group is an independent risk factor for GC, as H. pylori infection was an exclusion criterion for both cases and controls (Table 4).

There were no significant difference between sexes (Tables 1, 2, and 3), although numerous modifiable risk factors for GC, such as smoking and drinking habits, are more common in Korean males than in females, as demonstrated by Song et al. 2013, who found that the A allele was only a risk factor in females with fewer modifiable risk factors compared to males with more modifiable risk factors, confounding the effect of the A allele [30, 16]. We found no significant difference between blood groups regarding the clinicopathologic characteristics of GC in terms of TNM stage (American Joint Committee on Can-

cer 7th edition 2010), surgical access type (open vs. laparoscopic), and extent of gastrectomy (total gastrectomy, subtotal gastrectomy, other) (Table 3). This is likely because most cases were screen-detected EGC across all blood groups. Other studies showed an association between ABO blood groups and GC clinicopathological characteristics, including the association between group A and the diffuse histological subtype [10, 30]; however, other studies failed to show an association between ABO blood groups and the tumor site of origin [30, 44]. The prognostic impact of ABO blood groups on GC survival was investigated, and the results showed that group AB has the best prognostic outcome compared to non-AB blood groups, with group A having the worst prognosis [45].

The strengths of this study include the well-powered large sample and ethnic homogeneity, which mitigate the confounding effect of the discordant rate of the blood group distribution that is sensitive to geographical and ethnic variations. One limitation of this study is that the controls were blood donors, which may have led to selection bias because of the strict inclusion and exclusion criteria of blood banks, altering the risk of the controls, e.g., being younger, less obese, and suffering fewer comorbidities. However, this effect was mitigated by the fact both controls and cases had no history of H. pylori or peptic ulcer disease, and showed no significant differences regarding other modifiable (i.e., smoking and drinking status) and non-modifiable (i.e., sex and family history of GC) risk factors. Further limitations of the study are the potential residual confounding due to differences between cases and controls, all limitations and risk of bias inherent to the study design, and an inability to generalize the results to other populations.

Conclusion

This large-scale case-control study was conducted to investigate the nature of the association between ABO blood groups and GC risk. The results were consistent with those of previous studies showing that group A is a risk factor for GC, group O is a protective factor, and group B is a neutral factor. The most important finding of this study is that group AB was observed to be an independent risk factor for GC even when other confounding factors (e.g., H. pylori seropositivity, smoking and drinking habits, sex, age, BMI, comorbidities, and family history of GC) were controlled. These results provide a foundation for further epidemiological studies to determine the underlying etiological mechanism of the A antigen in GC carcinogen-

esis to identify targets for prevention by risk-modification strategies, therapy, and prognosis prediction.

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Ethics approval and consent to participate

Informed consent was obtained from all participants and IRB approval obtained from Saint Mary Catholic University Hospital, Seoul, Republic of Korea, as well as from King Fahd Medical City, Riyadh, KSA (IRB log number: 19-646E)

Conflict of Interest:

The authors declare no conflict of interest regarding this manuscript, and no funding was received for this manuscript from any public or private institution.

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