

Sex-specific differences in the association between ABO genotype and gastric cancer risk in a Korean population

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Abstract

Background Although previous studies have demonstrated an association between ABO blood group and the risk of gastric cancer (GC), only one study has identified these associations using the ABO genotype; however, that study did not evaluate sex differences in this association. The aim of the present study was to investigate whether there are sex-specific differences in the ABO genotype-associated risk of GC. In addition, we explored the association of the ABO genotype and the clinicopathologic characteristics of GC in a Korean population.

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Methods We conducted a large-scale case–control study of 3245 GC patients (2204 males, 1041 females) and 1700 controls (821 males, 879 females). The ABO genotype was determined by multicolor real-time polymerase chain reaction (PCR) using displacing probes.

Results As compared with genotype *OO*, genotypes *AA* and *AO* in females, but not in males, were associated with a significantly increased risk of GC (odds ratio [OR] 1.56 and 95 % confidence interval [CI] 1.08–2.26 for *AA*; OR 1.57 and 95 % CI 1.21–2.03 for *AO*). In a subgroup analysis, blood group A had a significantly increased risk of diffuse-type GC (OR 2.00, 95 % CI 1.43–2.78), but not of intestinal-type (OR 1.31, 95 % CI 0.96–1.79) or mixed-type GC (OR 1.43, 95 % CI 0.92–2.24).

Conclusion The ABO genotypes *AA* and *AO* were significantly associated with GC only in females and only for diffuse-type GC. These data suggest that the association between ABO blood group and GC risk may differ according to sex and histological type.

Keywords Gastric cancer · ABO genotype · Polymorphism · Sex-specific differences · Histological type

Introduction

According to the World Health Organization (WHO), gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer deaths in several areas, most notably Japan, Korea, and other Asian nations. Although the incidence and mortality of GC have been decreasing, it remains the most common cancer and a major public health issue in Korea [1].

Several factors, such as diet, work environment, exposure to *Helicobacter pylori*, and a history of stomach

disorders have been considered potential risk factors [2]. In addition, the relationship between ABO blood group and GC has been reported since the early 1900s, and a recent large prospective study demonstrated a significant association between ABO blood group and the risk of GC [3]. Although the results of other studies have been inconsistent [4–8], blood group A is recognized as an established risk factor for GC.

Recently, there has been renewed interest in the association between ABO blood group and cancer. A genome-wide association study (GWAS) identified pancreatic cancer susceptibility loci in the ABO gene [9]. Also, two studies in the Pancreatic Cancer Cohort Consortium found a lower risk of pancreatic cancer among individuals with the ABO blood genotype *OO* [10, 11]. Nakao et al. showed a statistically significant association between ABO genotype and GC risk using ABO genotyping in a Japanese population [12].

In addition, a sex-specific association between not only GC and conventional risk factors [13, 14], but also between ABO blood group and esophageal carcinoma and cardiac carcinoma, has been reported [15]. To our knowledge, no previous report has evaluated the association between ABO genotype and the risk of GC based on sex; thus, there remains a need to further investigate the interaction between sex and ABO genotype in GC.

Therefore, we conducted a large-scale case–control study to determine whether there are sex-specific differences in the ABO genotype-associated risk of GC, and to explore the association of the ABO genotype and the clinicopathologic characteristics of GC in a Korean population.

Methods

Subjects

The study population consisted of 3245 patients with newly diagnosed GC (cases). In all enrolled patients the disease was confirmed by pathological examination at Chonnam National University Hwasun Hospital between April 2004 and February 2010. Patients with secondary or recurrent tumors were excluded. GC was classified by anatomical site as cardia (International Classification of Diseases [ICD] 10th edition, C16.0) or non-cardia (C16.1–16.8) and by histological type; i.e., intestinal, diffuse, or mixed type.

The control group ($n = 1700$) consisted of participants in the Thyroid Disease Prevalence Study conducted from July 2004 to January 2006 in Yeonggwang and Muan counties of Jeollanam-do Province and in Namwon city of Jeollabuk-do Province, Korea [16]. That study selected 4,018 subjects randomly, using 5-year age strata and

gender, from the resident registration list of six areas in Namwon city and Yeonggwang and Muan counties. Of the total, after excluding deaths and other residents at the registered addresses, 3,486 subjects were eligible. Of those eligible, 1700 (48.8 % of the eligible subjects; 821 males and 879 females), underwent clinical examinations and ABO genotyping by the same method as that used in the present study [17]. At the time of their peripheral blood collections, all case and control subjects provided their informed consent to participate in this study. This study was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital in Hwasun, Korea.

Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's protocol. The ABO genotype was determined by multicolor real-time polymerase chain reaction (PCR) using displacing probes. The primers and probes were designed as described by Ruan et al. [18] and were synthesized and high performance liquid chromatography (HPLC)-purified by Bioneer (Daejeon, Korea). The reaction mixture included each 400 nM PCR primers for exon 6, 500 nM PCR primers for exon 7, 50 nM probes for A del and O del, 100 nM probes for A and B, 0.5 U *f*-Taq polymerase (Solgent, Daejeon, Korea), and 40 ng genomic DNA in 25- μ l reaction volumes. Real-time PCR was run on a Rotor-Gene 3000 (Corbett Research, Mortlake, Australia). The cycling conditions started with denaturation at 96 °C for 2 min, followed by 10 cycles of touchdown PCR (96 °C for 15 s, 68 °C with 1 °C/cycle decrease for 20 s, then 72 °C for 15 s) and 40 cycles of 95 °C for 15 s, 58 °C for 15 s, and 72 °C for 15 s. Fluorescence from all four channels (FAM, JOE, ROX, and Cy5) was recorded at the annealing step of 58 °C during the later 40 cycles.

Statistical analysis

The χ^2 test was used to evaluate differences for categorical variables in the demographic characteristics of the subjects. Adjusted odds ratios (ORs) and their 95 % confidence intervals (CIs) were calculated using logistic regression models, with adjustments for age, sex, and smoking and drinking habits to estimate the association between ABO blood group and GC. Heterogeneity was tested by a multivariable logistic regression model. Subjects for whom there were missing data for smoking and drinking habits, TNM stage, tumor site, and histological type were excluded from the interaction and subgroup analyses related to these variables. Subjects with the ABO phenotype *O* or

genotype *OO* were considered to have a baseline risk. A two-sided *p* value of <0.05 , not adjusted by Bonferroni correction, was initially considered statistically significant. Statistical analyses were calculated using SPSS version 16.0 (Chicago, IL, USA) and Cochrane Review Manager 5.1 version (The Nordic Cochrane Center, Copenhagen, Denmark).

Results

General characteristics of subjects

The characteristics of the 3245 GC cases and 1700 controls are summarized in Table 1. Cases and controls differed with respect to age and sex. We therefore adjusted for age and stratified by sex in the subsequent multivariable logistic regression analysis.

Table 1 General characteristics of subjects

	Controls	Gastric cancer cases
No.	1700	3245
Age, years (range)*	52.1 (19.9–76.0)	60.5 (20.6–87.3)
≤ 60 years	1117 (65.7)	1405 (43.3)
> 60 years	583 (34.3)	1840 (56.7)
Sex*		
Male	821 (48.3)	2204 (67.9)
Female	879 (51.7)	1041 (32.1)
Smoking		
Never	1000 (58.8)	1620 (49.9)
Ever	655 (38.5)	1532 (47.2)
Unknown	45 (2.6)	93 (2.9)
Drinking		
Never	706 (41.5)	1609 (49.6)
Ever	952 (56.0)	1538 (47.4)
Unknown	42 (2.5)	98 (3.0)
TNM stage		
I		1900 (58.6)
II		429 (13.2)
III		334 (10.3)
IV		464 (14.3)
Unspecified stage		118 (3.6)
Tumor location		
Cardia		140 (4.3)
Non-cardia		3086 (95.1)
Unknown		19 (0.6)
Histological type		
Intestinal		1932 (59.5)
Diffuse		781 (24.1)
Mixed		370 (11.4)
Unspecified type		162 (5)

* Gastric cancer cases compared with controls, $p < 0.01$

ABO blood group and gastric cancer risk

Table 2 shows the distribution of ABO blood groups and their association with GC risk. The allele frequencies of *O*, *A*, and *B* were 50.1, 29.5, and 20.4 %, respectively, in controls and 49.4, 32.0, and 18.5 %, respectively, in GC patients. These results were consistent with previous studies [19]. As compared with blood group *O*, blood group *A*, but not groups *AB* or *B*, was associated with a significantly increased risk of GC overall (adjusted OR 1.28 and 95 % CI 1.09–1.50). There was a significant sex difference in the effect of ABO blood group on GC risk (*p* value for interaction 0.03, data not shown). In an analysis stratified by sex, an increased risk of GC was observed only in female GC patients with blood group *A* (OR 1.57, 95 % CI 1.22–2.01). A similar pattern was observed for the association between ABO genotype and GC (Fig. 1), where an elevation in risk was associated with females of genotype *AA* (OR 1.56, 95 % CI 1.08–2.26) and *AO* (OR 1.57, 95 % CI 1.21–2.03).

Subgroup analysis for the ABO blood group

The associations between ABO blood group and GC were further evaluated by stratified analysis of age, smoking, drinking, tumor location, TNM stage, and histological type. No association between ABO blood group and the clinicopathologic characteristics of GC was found in males (Fig. 2). In contrast, in females (Fig. 3), the OR for blood group *A* was higher in patients with diffuse-type GC (OR 2.00, 95 % CI 1.43–2.78) than in those with intestinal-type (OR 1.31, 95 % CI 0.96–1.79) or mixed-type GC (OR 1.43, 95 % CI 0.92–2.24) (*p* for interaction 0.04, I^2 for heterogeneity 69.8 %). However, significant effects disappeared after Bonferroni correction for multiple testing. Although the effect of blood group *A* was larger in the patients with a drinking habit (OR 1.97, 95 % CI 1.16–3.37) than in those without a drinking habit (OR 1.50, 95 % CI 1.13–2.00), and larger in patients with non-cardia GC (OR 1.63, 95 % CI 1.27–2.08) than in those with cardia GC (OR 1.16, 95 % CI 0.42–3.25), these factors did not modify the association between the ABO blood group and GC risk.

Subgroup analysis according to the ABO genotype

Results of subgroup analysis according to the ABO genotype were similar to those for the ABO phenotype. No significant differences were found in any stratified group of male subjects. Otherwise, the risk of GC in patients with the *AA* genotype was higher than other genotypes in those aged 60 years or less, and in the non-smoking, non-alcohol consumption group, and the risk of GC in patients with the *AO* genotype was higher in most of the stratified groups of

Table 2 Distribution of ABO blood groups and their association with gastric cancer (GC) risk

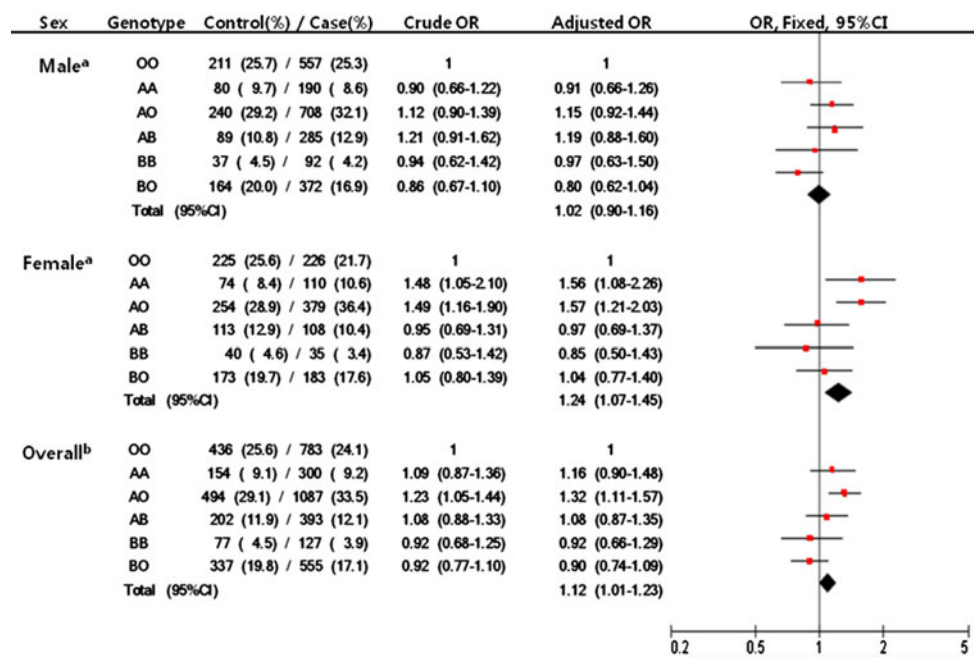
	Controls (%)	GC (%)	OR (95 % CI)		
			Male ^a	Female ^a	Overall ^b
O	436 (25.6)	783 (24.1)	1	1	1
A	648 (38.1)	1387 (42.7)	1.09 (0.88–1.35)	1.57 (1.22–2.01)	1.28 (1.09–1.50)
AB	202 (11.9)	393 (12.1)	1.19 (0.88–1.60)	0.97 (0.69–1.37)	1.08 (0.87–1.35)
B	414 (24.4)	682 (21.0)	0.83 (0.66–1.06)	1.02 (0.77–1.35)	0.91 (0.75–1.09)
<i>p</i> value			0.1	<0.01	<0.01

OR odds ratio, CI confidence interval

^a Multivariable adjustment by age and smoking and drinking habits

^b Multivariable adjustment by age, sex and smoking and drinking habits

Fig. 1 Multivariable-adjusted ORs (95 % CIs) of gastric cancer risk associated with ABO genotype. The estimates of ORs and their 95 % CIs are plotted with boxes and horizontal lines. Diamonds pooled OR and its 95 % CI, OR odds ratio, CI confidence interval; ^amultivariable adjustment by age and smoking and drinking habits, ^bmultivariable adjustment by age, sex and smoking and drinking habits



female subjects, excluding those stratified by smoking habit, and those with cardia-GC, and those with intestinal- and mixed-type GC (data not shown). The risk of genotype AO (OR 2.13, 95 % CI 1.51–3.01) for diffuse-type GC was the largest across all genotypes or histological types in females. There was no interaction between ABO genotype and the clinicopathologic variables of age, smoking, drinking, tumor location, and TNM stage in female patients, but histological type did show an association with ABO genotype ($p = 0.03$, $I^2 = 70.8\%$) as well as with ABO phenotype (data not shown).

Discussion

This case–control study included a large sample (3245 GC patients and 1700 controls) of a single population, and aimed to evaluate a possible association between ABO

genotype and GC risk. To our knowledge, this is the second report to examine the association between ABO genotype and susceptibility to GC. We found a significantly higher risk of GC for the AA and AO genotypes as compared with the OO genotype in females, but not in males.

The human ABO blood group is determined by the ABO gene located on chromosome 9. The ABO gene locus can be considered to have three alleles: A, B, and O. With three alleles, there are six possible genotypes (AA, AO, BB, BO, AB, and OO). For the determination of ABO genotypes, several methods, such as PCR–restriction fragment length polymorphism (RFLP), allele-specific (AS)-PCR, and sequencing have been introduced in transfusion medicine. Of these, real-time PCR is considered to be the best method for studies of large populations [17].

In the present study, ABO blood group was not determined by a serological method, but instead it was determined from ABO genotype data analyzed by a multicolor

Fig. 2 Subgroup analysis of ABO blood groups in males. The estimates of ORs and 95 % CIs are plotted with boxes and horizontal lines. Diamonds pooled OR and its 95 % CI, OR odds ratio adjusted for age, CI confidence interval, I² heterogeneity index

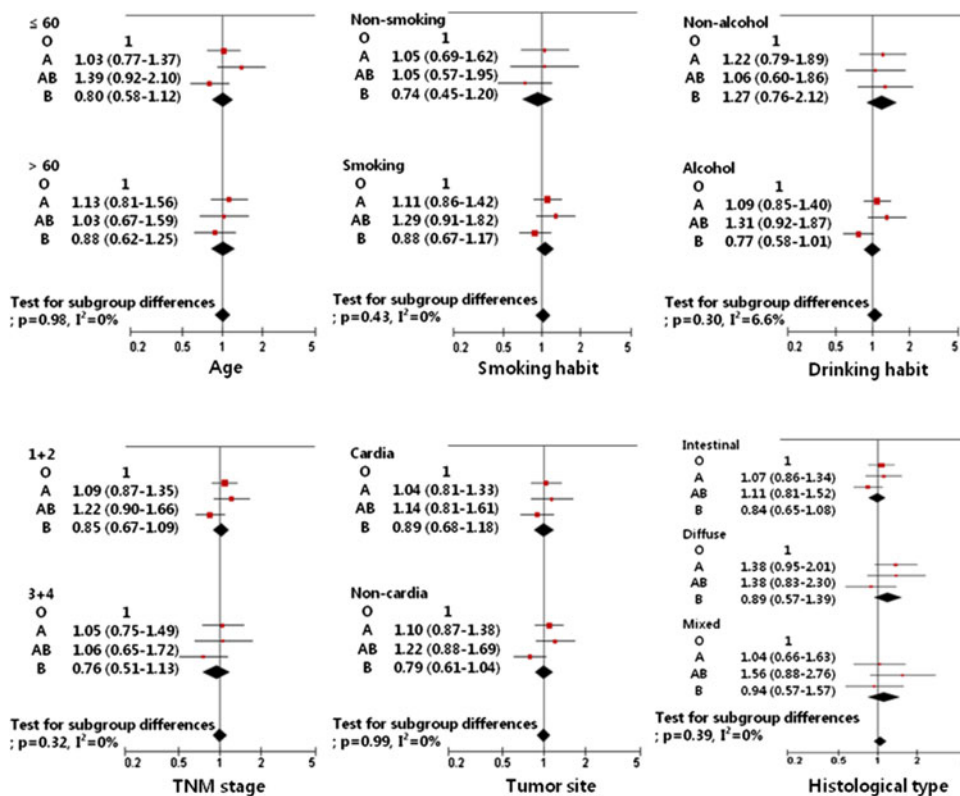
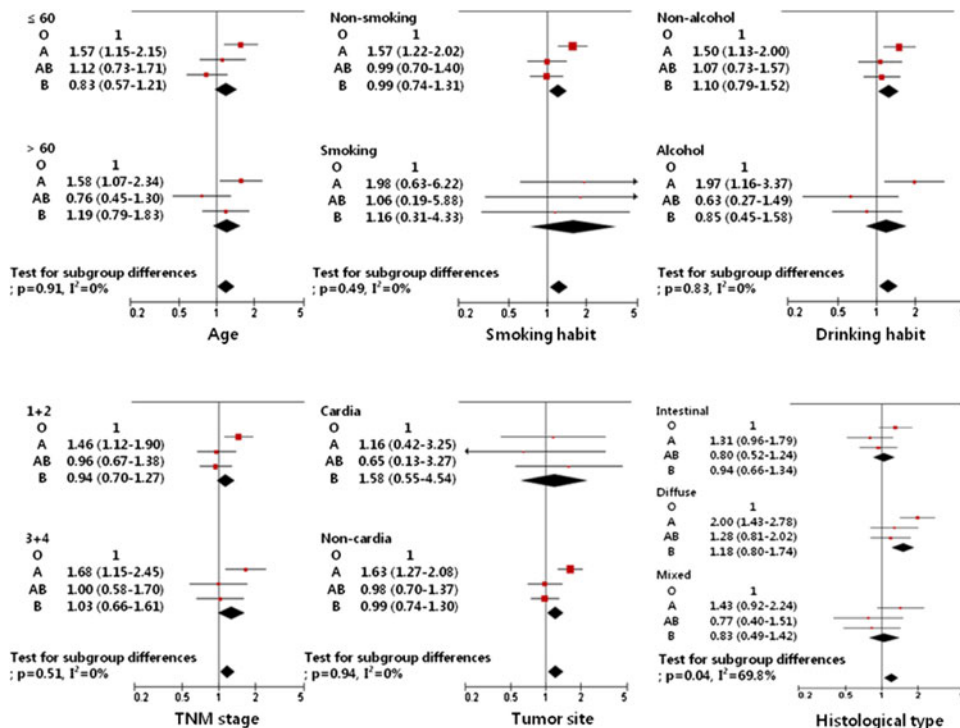


Fig. 3 Subgroup analysis of ABO blood groups in females. The estimates of ORs and 95 % CIs are plotted with boxes and horizontal lines. Diamonds pooled OR and its 95 % CI, OR odds ratio adjusted for age, CI confidence interval, I² heterogeneity index



real-time PCR technique. Thus, there is the possibility of a discrepancy between serological phenotypes and those predicted from genotypes. However, the error rate is considered to be negligible because the ABO subgroup

frequency in the general population of southwestern Korea included in this study, (Yeonggwang and Muan counties and Namwon city) was only 0.114 % [19]. It was also reported that the discordance rates between genotypes and

phenotypes defined as groups *A*, *B*, *AB*, and *O* were 0.18 % (2/1134 samples) in a Japanese population and 0.12 % (2/1700) in our previous study [17, 20].

In epidemiologic studies of the association between ABO genotype and GC, it should be noted that the distribution of ABO blood groups varies geographically and among ethnic groups [15]. Additionally, there is substantial inter-individual variation in the susceptibility to genetic events. In the present study, we selected GC and control samples from residents in the same province to avoid such a sampling error.

The association between ABO blood group and cancers has been examined extensively. Blood group *A* is an established risk factor for GC [4, 5, 7, 8], although these results are controversial [15, 21]. Recently, a large-scale prospective cohort study identified a significant association between serological ABO blood group and the risk of GC in a Western population [3]. In addition, Nakao et al. [12] found that, in a Japanese population, ABO genotype was associated with a significantly increased risk of GC, which tended to increase with addition of the *A* allele. These results are consistent with our findings.

In addition to GC risk, an association between ABO blood type and other types of cancer has been reported. Compared with non-*O* (*A*, *AB*, and *B*) individuals, *O* group individuals have a 14 % reduced risk of squamous cell carcinoma and a 4 % reduced risk of basal cell carcinoma [22]. The *B* antigen has been linked to an increased risk of ovarian cancer [23]. However, the mechanism by which genetic variants in the ABO gene locus influence the risk of various types of cancers is not completely understood.

The most meaningful finding in our study was the sex-specific difference in the effect of the ABO blood group on GC risk. Although a significant association between ABO blood group *A* and GC was evident in the entire subject population, in a subgroup analysis by sex, the association was found only in females. The reason for this difference in GC remains unknown. However, it may be due to the differing prevalence of environmental risk factors such as *H. pylori* infection and dietary, smoking, and alcohol habits. Previous studies have shown that *H. pylori* infection is closely associated with blood groups *A* and *O*, and that smoking and male sex function as protective factors [24, 25]. In Korea, males may have more frequent and prolonged exposure to environmental factors such as a high-risk diet, heavy smoking, and alcohol drinking than females, owing to their different social activities. Indeed, the effect of some specific factors, including genetic and hormonal factors, on GC risk was shown to be relatively stronger in females than males [13]. Thus, we postulated that the attributable risk of GC within blood group *A* was relatively higher in females than in males.

In our subgroup analysis by histological type, blood group *A* in females was associated with a significantly increased risk of diffuse-type, but not intestinal-type or mixed-type GC. Intestinal-type and diffuse-type GC have distinct characteristics [2, 26]. Many genetic and epigenetic changes are differentially observed in these two histological types of GC, and genetic factors may contribute more to diffuse-type than to intestinal-type [27]. Nakao et al. [12] also examined the effect of ABO blood group on GC histological types. They indicated a significant association of blood group with GC only for diffuse-type, and a weak association of genotype with intestinal-type. However, in our study, no discrepancy between phenotype and genotype was found. Our results showed a consistently significant association of GC with ABO type in females, and of diffuse-type with the *AO* genotype. Because there is a lack of information regarding the relationship between ABO blood groups and the clinicopathologic characteristics of GC, further studies are needed to confirm these findings.

The present study has some limitations. First, we could not obtain information from subjects on the presence or absence of an *H. pylori* infection history. Second, we could not rule out the possibility that differential misclassification bias may have occurred because we retrospectively collected data about smoking and alcohol from electronic medical records in the GC cases, whereas cross-sectional surveys were used to collect data about these parameters in the controls. Third, although this study had a relatively large sample size, the numbers of subjects in the subgroup analyses were small.

In conclusion, the ABO genotypes *AA* and *AO* were significantly associated with GC in females and the *AO* genotype was significantly associated with diffuse-type GC. These data suggest that the association between ABO blood group and GC risk may differ according to sex and histological type.

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