Research Article

Cancer Epidemiology, Biomarkers & Prevention

ABO Genotype and the Risk of Gastric Cancer, Atrophic Gastritis, and *Helicobacter pylori* Infection

Makoto Nakao[1,2], Keitaro Matsuo[1,3], Hidemi Ito[1], Kohei Shitara[4], Satoyo Hosono[1], Miki Watanabe[1], Seiji Ito[5], Akira Sawaki[6], Shinsuke Iida[2], Shigeki Sato[2], Yasushi Yatabe[7], Kenji Yamao[6], Ryuzo Ueda[2], Kazuo Tajima[1], Nobuyuki Hamajima[8], and Hideo Tanaka[1,3]

Abstract

Background: Although several studies have investigated the association between ABO blood type and risk of gastric cancer (GC), atrophic gastritis (AG), and *Helicobacter pylori* (HP) infection, no study has investigated these associations by using *ABO* genotype.

Methods: We conducted a case–control study in 703 patients with GC and 1,465 noncancer patients. We also conducted a cross-sectional study by using 1,406 of these 1,465 controls, who were examined for pepsinogens and anti-HP IgG antibody levels in serum. *ABO* genotype was determined from single nucleotide polymorphisms in *ABO* gene. We used rs8176719 to mark the *O* allele, and rs8176746 and rs8176747 to mark the *B* allele. ORs and 95% CIs were calculated by a multivariate logistic model.

Results: We observed significant associations between *ABO* genotype and GC, AG, and HP infection. ORs (95% CIs) of GC were 0.70 (0.50–0.99) for *OO* and 0.53 (0.36–0.77) for *BO* relative to *AA* genotype. An increased risk of GC was observed with addition of the *A* allele ($P_{trend} < 0.001$), and a decreased risk with that of the *B* allele ($P_{trend} = 0.023$). An OR of AG was 0.73 (95% CI, 0.53–0.99) for blood type B relative to blood type A, and an OR of HP infection was 0.39 (95% CI, 0.17–0.87) for *BB* relative to *AA* genotype.

Conclusion: This study identified a statistically significant association between *ABO* genotype and GC risk. In addition, *ABO* gene locus may influence AG prevalence and HP infection.

Impact: Further studies are necessary to confirm these findings. *Cancer Epidemiol Biomarkers Prev; 20(8); 1665–72. ©2011 AACR.*

Introduction

Although the age-standardized incidence of gastric cancer (GC) in Japan is decreasing, it remains one of the most common cancers (1). Worldwide, GC is still the fourth most common cancer and the second most common cause of cancer death (2, 3). Although the major risk factors of GC have been established, specifically *Helicobacter pylori* (HP) infection, male sex, family history of GC, and smoking (3), epidemiologic studies to explore GC risk still play an important role in identifying GC high-risk groups and ultimately in decreasing the number of GC deaths.

A recent large prospective cohort study identified a statistically significant association between ABO blood type and the risk of GC in a Western population (4). Although the association between ABO blood type and GC risk has been investigated for more than half a century, results have been somewhat conflicting (5–9). Meanwhile, although several studies have used single nucleotide polymorphisms (SNP) within the *ABO* gene locus to show a statistically significant association between *ABO* genotype and risk of pancreatic cancer (10–12), previous studies of the association between GC risk and ABO blood type have used serotype-derived ABO blood type, and not *ABO* genotype.

Here, we conducted a case–control study to assess the impact of *ABO* genotype on the risk of GC among a Japanese population. In addition, because HP infection is a well-established risk factor for GC and the inflammation caused by HP infection is thought to cause atrophic gastritis (AG) and GC (13–16), we also assessed the difference among *ABO* genotypes in AG prevalence and HP infection.

Authors' Affiliations: [1]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Chikusa-ku, [2]Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Science, Mizuho-cho, Mizuho-ku, [3]Department of Epidemiology, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Aichi; [4]Department of Medical Oncology, Aichi Cancer Center Central Hospital, [5]Department of Gastroenterological Surgery, Aichi Cancer Center Central Hospital, [6]Department of Gastroenterology, Aichi Cancer Center Central Hospital, [7]Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Central Hospital, Chikusa-ku, Nagoya; and [8]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Aichi, Japan

Corresponding Author: Keitaro Matsuo, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Phone: 81-52-762-6111 ext. 7013; Fax: +81-52-763-5233; E-mail: kmatsuo@aichi-cc.jp

doi: 10.1158/1055-9965.EPI-11-0213

Materials and Methods

Study population

Cases comprised 703 GC patients with no prior history of cancer who were diagnosed at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan, between January 2001 and November 2005. Control subjects comprised 1,465 randomly selected noncancer outpatient visitors to ACCH during the same period who had no history of any cancer. All subjects making their first visit to ACCH between January 2001 and November 2005 were enrolled at first visit in the Hospital-based Epidemiological Research Program II at ACCH (HERPACC-II). The framework of HERPACC-II has been described elsewhere (17, 18). Briefly, all first-visit outpatients at ACCH ages 20 to 79 years are asked to fill out a self-administered questionnaire regarding their lifestyle before development of the current symptoms. Responses are checked by trained interviewers. Outpatients are also asked to provide a 7-mL blood sample. Approximately 95% of eligible subjects complete the questionnaire and 50% provide blood samples. All data are loaded into the HERPACC database, which is periodically synchronized with the hospital cancer registry system to update the data on cancer incidence. Approximately 35% of subjects (46% of male subjects and 28% of female subjects) were diagnosed with cancer within a year of first visit. In this study, we defined patients diagnosed with GC within a year of first visit as the case population. Among cases, histologic information was available for 98.15% (310 cases, intestinal type; 380 cases, diffuse type; and 13 cases, unknown). Our previous study showed that the lifestyle patterns of first-visit outpatients at ACCH corresponded with those of individuals randomly selected from Nagoya's general population, confirming external validity for the study (19). This study was approved by the Ethics Committee of Aichi Cancer Center and informed consent to participate was obtained at first visit from all participants.

Selection and genotyping of ABO blood group allele

In this study, we examined 3 loci on the *ABO* gene, rs8176719, rs8176746, and rs8176747. Those loci are responsible for the ABO blood group phenotype in the Japanese population. Examination of the cDNA nucleotide sequence of the *ABO* gene on chromosome 9q34.2 revealed the following for the Japanese population: a 261G deletion in exon 6 (rs8176719) results in the *O* allele, and C796A and G803C in exon 7 (rs8176746 and rs8176747, respectively) distinguish the *B* allele from *A* allele (20–23). DNA of each subject was extracted from the buffy-coat fraction by using the DNA Blood Mini Kit (Qiagen). All loci were examined by TaqMan assays (Applied Biosystems). The principle of the TaqMan real-time PCR assay system using fluorogenic probes and 5′ nuclease has been described by Livak (24). Custom probes and primers were specifically designed for the 3′ loci. Genotyping for the *ABO* 261G deletion (rs8176719) was done by PCR with 5′-CCTGTGTGGATGTGCAGTAGGA-3′ and 5′-CGTTGAGGATGTCGATGTTGAA-3′ primers, and Fam-TCCTCGTGGTGACCCCTTGGC-TAMRA and Vic-ATGTCCTCGTGGTACCCCTTGGCT-TAMRA probes (21). Genotyping for the *ABO* C796A and G803C (rs876746 and rs876747, respectively) was done by PCR with 5′-CTGCACCTCTTGCACCGAC-3′ and 5′-AGGCCTTCACCTACGAGCG-3′ primers, and Fam-CCCGAAGAACCCCCCCAGGTAGTAGAAA-TAMRA and Vic-CCCGAAGAACGCCCCCATGTAGTAGAAA-TAMRA probes (21). All of the assays were carried out in 96-well PCR plates by using a 7500 Fast Real-time PCR System with the corresponding 7500 Fast System SDS software (Applied Biosystems). Amplification reactions were done in duplicate with 30 ng (5 μL) of template DNA, 2× TaqMan Universal Master Mix buffer (Applied Biosystems), and 20× primer and probe mix (Applied Biosystems). Thermal cycling was carried out under the following conditions: denaturation at 95°C for 20 seconds followed by 40 cycles of 95°C for 3 seconds and 62°C for 30 seconds. In our laboratory, the quality of genotyping is routinely statistically assessed by using the Hardy–Weinberg test and retyping of a random sampling of 5% of subjects. We also confirmed that there were no allelic distributions among the controls that departed from the Hardy–Weinberg frequency.

AG and HP infection assessment

Among the 1,465 controls, 1,406 were available for measurement of serum pepsinogens and IgG levels for HP. Serum pepsinogens (PG) were measured by chemiluminescence enzyme immunoassay, and gastric mucosal atrophy was defined by a PG I value of 70 ng/mL or less and PG I/PG II $\leq$ 3 (13, 25). Serum IgG levels for HP were measured by a commercially available direct ELISA kit ("E Plate 'Eiken' HP Antibody" Eiken Kagaku). This ELISA kit was developed in Japan by using the antigen extracted from a domestic strain in Japan and is commonly used in medical studies (26, 27). Positivity for HP infection was defined as an anti-HP IgG antibody level greater than 10 U/mL in serum.

Assessment of lifestyle exposures

Exposure to potential GC risk factors was assessed from the self-administered questionnaire results, which were completed before diagnosis during the first visit to ACCH and reviewed by trained interviewers. Subjects were specifically questioned about their lifestyle before the onset of the symptoms which impelled their visit to ACCH. Daily alcohol consumption in grams was determined by summing the pure alcohol amount in the average daily consumption of Japanese sake (rice wine), shochu (distilled spirit), beer, wine and whiskey, with 1 cup of Japanese sake (180 mL) considered equivalent to 23 g of ethanol, 1 drink of shochu (108 mL) to 23 g, 1 large bottle of beer (633 mL) to 23g, 1 glass of wine (80 mL) to 10 g, and 1 shot of whiskey (28.5 mL) to 11.5 g. Cumulative smoking exposure was measured in pack-years, the product of the average number of packs per day and the

Table 1. Characteristics of GC case and control

	Case (%); $n = 703$	Control (%); $n = 1{,}465$	P^a
Age			
<40	34 (4.84)	75 (5.12)	0.759
≥40 but <50	72 (10.24)	147 (10.03)	
≥50 but <60	246 (34.99)	479 (32.70)	
≥60 but <70	214 (30.44)	484 (33.04)	
≥70	137 (19.49)	280 19.11)	
Sex			
Male	527 (74.96)	1,097 (74.88)	0.966
Female	176 (25.04)	368 (25.12)	
Cigarette pack-years			
<5	239 (34.00)	638 (43.55)	<0.001
≥5 but <20	84 (11.95)	206 14.06)	
≥20 but <40	160 (22.76)	308 (21.02)	
≥40	213 (30.30)	304 (20.75)	
Unknown	7 (1.00)	9 (0.61)	
Drinking, g ethanol/day			
Nondrinking	229 (32.57)	488 (33.31)	0.002
<23	169 (24.04)	425 (29.01)	
≥23 but <46	160 (22.76)	342 (23.34)	
≥46	134 (19.06)	193 (13.17)	
Unknown	11 (1.56)	17 (1.16)	
Family history of GC			
No	548 (77.95)	1,190 (81.23)	0.051
Yes	155 (22.05)	270 (18.43)	
Unknown	0 (0.00)	5 (0.34)	

[a]χ^2 test.

number of years of smoking. Family history of GC was considered positive when at least one parent or sibling had a history of GC.

Statistical analysis

All statistical analyses were carried out by Stata version 10 (Stata Corp.). $P < 0.05$ was considered statistically significant. Differences in characteristics between cases and controls were assessed by the χ^2 test. ORs and 95% CIs were estimated by using an unconditional logistic regression model adjusted for potential confounders. Potential confounders considered in multivariate analysis were age, sex, pack-years of smoking (<5, <20, <40, or ≥41), drinking habit (nondrinker, <23, <46, or ≥46 g/day), and family history of GC (yes or no). Accordance with Hardy–Weinberg equilibrium was assessed by the χ^2 test.

Results

Background characteristics of GC cases and controls are shown in Table 1. Patients with GC had a significantly higher ratio of heavy smokers ($P < 0.001$) and heavy drinkers ($P = 0.002$), and a marginally higher ratio of a family history of GC ($P = 0.051$). Characteristics of the 1,406 participants examined for serum anti-HP IgG antibody and pepsinogens levels were closely similar to those of the total 1,465 noncancer participants (Table 2). High age, male sex, and heavy smoking were more common in HP-positive than -negative patients, whereas high age and HP infection were more common in AG-positive than -negative patients.

Using rs8176719 as a marker for the *O* allele, and rs8176746 and rs8176747 for the *B* allele, all participants' 2 *ABO* alleles were inferred. Allele frequencies of the *O*, *A*, and *B* allele among the noncancer control subjects were 54.64%, 28.33%, and 17.03%, respectively. These frequencies were consistent with information from the HapMap project and previous studies (22, 23, 28).

We assessed the risk of GC according to ABO blood type and *ABO* genotype among all study participants (Tables 3 and 4). In addition, we also assessed the risk of AG prevalence and HP infection according to ABO blood type and *ABO* genotype among the 1,406 noncancer participants. Compared with individuals with blood type A, those with blood type B were at lower risk of GC (OR = 0.60; CI, 0.46–0.78) and AG (OR = 0.73; CI, 0.53–0.99). In genotype analysis, ORs of GC relative to that of *AA* were 0.85 (CI, 0.60–1.18) for *AO*, 0.70 (CI, 0.50–0.99) for *OO*, 0.91 (CI, 0.61–1.37) for *AB*, 0.53 (CI, 0.36–0.77) for *BO*, and 0.48

Table 2. Characteristics of noncancer 1,406 participants according to HP infection status and AG status

	Serum pepsinogens and anti-HP IgG antibody measurable participants (%); $n = 1,406$	HP-positive (%); $n = 798$	HP-negative (%), $n = 608$	P^a	AG case (%); $n = 496$	AG-negative (%); $n = 910$	P^a
Age							
<40	74 (5.26)	18 (2.26)	56 (9.21)	<0.001	4 (0.81)	70 (7.69)	<0.001
≥40 but <50	142 (10.10)	52 (6.52)	90 (14.80)		18 (3.63)	124 (13.63)	
≥50 but <60	466 (33.14)	273 (34.21)	193 (31.74)		144 (29.03)	322 (35.38)	
≥60 but <70	460 (32.72)	292 (36.59)	168 (27.63)		194 (39.11)	266 (29.23)	
≥70	264 (18.78)	163 (20.43)	101 (16.61)		136 (27.42)	128 (14.07)	
Sex							
Male	1,062 (75.53)	628 (78.70)	434 (71.38)	0.002	388 (78.23)	674 (74.07)	0.083
Female	344 (24.47)	170 (21.30)	174 (28.62)		108 (21.77)	236 (25.93)	
Cigarette pack-years							
<5	605 (43.03)	321 (40.23)	284 (46.71)	0.004	209 (42.14)	396 (43.52)	0.258
≥5 but <20	200 (14.22)	108 (13.53)	92 (15.13)		69 (13.91)	131 (14.40)	
≥20 but <40	301 (21.41)	175 (21.93)	126 (20.72)		99 (19.96)	202 (22.20)	
≥40	291 (20.70)	191 (23.93)	100 (16.45)		117 (23.59)	174 (19.12)	
Unknown	9 (0.64)	3 (0.38)	6 (0.99)		2 (0.40)	7 (0.77)	
Drinking, g ethanol/day							
Nondrinking	457 (32.50)	255 (31.95)	202 (33.22)	0.321	162 (32.66)	295 (32.42)	0.762
<23	416 (29.59)	227 (28.45)	189 (31.09)		139 (28.02)	277 (30.44)	
≥23 but <46	330 (23.47)	189 (23.68)	141 (23.19)		119 (23.99)	211 (23.19)	
≥46	189 (13.44)	118 (14.79)	71 (11.68)		71 (14.31)	118 (12.97)	
Unknown	14 (1.00)	9 (1.13)	5 (0.82)		5 (1.01)	9 (0.99)	
Family history of GC							
No	1,146 (81.51)	643 (80.58)	503 (82.73)	0.245	394 (79.44)	752 (82.64)	0.118
Yes	258 (18.35)	155 (19.42)	103 (16.94)		102 (20.56)	156 (17.14)	
Unknown	2 (0.14)	0 (0.00)	2 (0.33)		0 (0.00)	2 (0.22)	
HP		-			< 0.001		
Positive	798 (56.76)				448 (90.32)	350 (38.46)	<0.001
Negative	608 (43.24)				48 (9.68)	560 (61.54)	

[a] χ^2 test.

Table 3. Age- and sex-adjusted, and multivariable-adjusted ORs (95% CIs) for incident GC HP infection and AG by genotype-derived ABO blood type

	A	O	AB	B
GC				
No. of cases (%)/controls (%)	319 (45.4)/572 (39.0)	194 (27.6)/428 (29.2)	81 (11.5)/141 (9.6)	109 (15.5)/324 (22.1)
Age- and sex-adjusted OR	1 (ref.)	0.81 (0.65–1.01)	1.03 (0.76–1.40)	0.60 (0.47–0.78)
Multivariable-adjusted OR[a]	1 (ref.)	0.80 (0.64–1.00)	1.4 (0.76–1.42)	0.60 (0.46–0.78)
AG				
No. of cases (%)/controls (%)	211 (42.5)/341 (37.5)	141 (28.4)/270 (29.7)	45 (9.1)/88 (9.7)	99 (20.0)/211 (23.2)
Age- and sex-adjusted OR	1 (ref.)	0.86 (0.65–1.13)	0.83 (0.55–1.26)	0.73 (0.54–0.99)
Multivariable-adjusted OR[a]	1 (ref.)	0.87 (0.66–1.14)	0.84 (0.55–1.27)	0.73 (0.53–0.99)
HP				
No. of cases (%)/controls (%)	318 (39.9)/234 (38.5)	241 (30.2)/170 (28.0)	70 (8.8)/63 (10.4)	169 (21.2)/141 (23.2)
Age- and sex-adjusted OR	1 (ref.)	1.09 (0.84–1.42)	0.83 (0.56–1.23)	0.88 (0.66–1.17)
Multivariable-adjusted OR[a]	1 (ref.)	1.11 (0.85–1.45)	0.84 (0.57–1.24)	0.89 (0.67–1.19)

[a]Multivariable adjustment by age, sex, smoking status, drinking habit, and family history of GC.

Table 4. Muitivariable-adjusted ORs (95% CIs) for incident GC, HP infection and AG by genotype-derived *ABO* blood group allele

Second allele	First allele		
	A	***O***	***B***
A			
GC			
No. of cases (%)/controls (%)	74 (10.5)/117 (8.0)	245 (34.9)/455 (31.1)	81 (11.5)/141 (9.6)
Multivariable-adjusted OR[a]	1 (ref.)	0.85 (0.60–1.18)	0.91 (0.61–1.37)
AG			
No. of cases (%)/controls (%)	43 (8.7)/68 (7.5)	168 (33.9)/273 (30.0)	45 (9.07)/88 (9.7)
Multivariable-adjusted OR[a]	1 (ref.)	0.91 (0.58–1.43)	0.78 (0.45–1.35)
HP			
No. of cases (%)/controls (%)	69 (8.7)/42 (6.9)	249 (31.2)/192 (31.6)	63 (10.4)/70 (8.8)
Multivariable-adjusted OR[a]	1 (ref.)	0.73 (0.47–1.13)	0.65 (0.38–1.10)
O			
GC			
No. of cases (%)/controls (%)	–	194 (27.6)/428 (29.2)	98 (13.9)/290 (19.8)
Multivariable-adjusted OR[a]		0.70 (0.50–0.99)	0.53 (0.36–0.77)
AG			
No. of cases (%)/controls (%)	–	141 (28.4)/270 (29.7)	87 (17.5)/189 (20.8)
Multivariable-adjusted OR[a]		0.80 (0.51–1.27)	0.65 (0.40–1.06)
HP			
No. of cases (%)/controls (%)	–	241 (30.2)/170 (28.0)	155 (19.4)/121 (19.9)
Multivariable-adjusted OR[a]		0.86 (0.55–1.34)	0.74 (0.46–1.19)
B			
GC			
No. of cases (%)/controls (%)	–	–	11 (1.6)/34 (2.3)
Multivariable-adjusted OR[a]			0.48 (0.23–1.02)
AG			
No. of cases (%)/controls (%)	–	–	12 (2.42)/22 (2.42)
Multivariable-adjusted OR[a]			0.86 (0.38–1.99)
HP			
No. of cases (%)/controls (%)	–	–	14 (1.8)/20 (3.3)
Multivariable-adjusted OR[a]			0.39 (0.17–0.87)

[a]Multivariable adjustment by age, sex, smoking status, drinking habit, and family history of GC.

(CI, 0.23–1.02) for *BB*. In addition, compared with individuals with the *AA* genotype, those with the *BB* genotype were at lower risk of HP infection (OR = 0.39, CI = 0.17–0.87).

An increased risk of GC was observed with the addition of the *A* allele ($P_{trend} < 0.001$; Table 5) and a decreased risk with that of the *B* allele ($P_{trend} = 0.023$). Although an increased risk of AG was suggested with addition of the *A* allele ($P_{trend} = 0.071$), no relation was seen with the risk of HP infection ($P_{trend} = 0.617$). Moreover, a decreased risk of HP infection was suggested with the addition of the *B* allele ($P_{trend} = 0.052$), but no relation was seen between the risk of AG and addition of the *B* allele ($P_{trend} = 0.136$).

To explore difference between histologic subtypes (diffuse type and intestinal type), we also carried out subgroup analysis according to histologic subtypes. About diffuse-type GC risk, compared with subjects with blood type A, those with O, AB, and B blood types had ORs of 0.66 (CI, 0.50–0.88), 0.98 (CI, 0.67–1.43), and 0.52 (CI, 0.37–0.74), respectively. On the contrary, regarding the intestinal-type GC risk, compared with subjects with blood type A, those with O, AB, and B blood types had ORs of 1.04 (CI, 0.77–0.1.41), 1.16 (CI, 0.75–1.80), and 0.74 (CI, 0.51–1.05), respectively. Similarly, in genotype analysis, there was only a weak association between intestinal-type GC and *ABO* genotype.

Discussion

In this study, we found that the risk of GC was higher among those with the blood type A than those with blood type B in a Japanese population. In addition, we observed suggestive associations between *ABO* blood group alleles

Table 5. Age- and sex-adjusted, and multivariable-adjusted ORs (95% CIs) for incident GC, HP infection, and AG with the addition of *A* allele

	X, X[a]	*A, X*[a]	*A, A*	P_{trend}
GC				
No. of cases/controls	303/752	326/596	74/117	
Age- and sex-adjusted OR	1 (ref.)	1.36 (1.12–1.64)	1.56 (1.13–2.15)	<0.001
Multivariable-adjusted OR[b]	1 (ref.)	1.37 (1.13–1.67)	1.59 (1.15–2.21)	<0.001
AG				
No. of case/AG negative	240/481	213/361	43/68	
Age- and sex-adjusted OR	1 (ref.)	1.18 (0.93–1.50)	1.34 (0.87–2.07)	0.069
Multivariable-adjusted OR[b]	1 (ref.)	1.18 (0.93–1.50)	1.34 (0.87–2.07)	0.071
HP				
No. of cases/controls	311/410	255/319	42/69	
Age- and sex-adjusted OR	1 (ref.)	0.92 (0.73–1.16)	1.29 (0.84–1.97)	0.585
Multivariable-adjusted OR[b]	1 (ref.)	0.91 (0.72–1.14)	1.28 (0.84–1.96)	0.617

[a]*X* represents *O* or *B* allele.
[b]Multivariable adjustment by age, sex, smoking status, drinking habit, and family history of GC.

and the risk of AG and HP infection. To our knowledge, this is the first study to indicate a correlation between SNPs at *ABO* gene loci and the development of GC, AG, and HP infection.

Although the association between ABO blood type and many diseases has been investigated for more than half a century (29, 30), findings to date have been of little practical clinical or disease prevention value. In particular, no clear evidence about the association between ABO blood type and risk of GC, AG, and HP infection has been produced (6–9, 13, 31–33). Meanwhile, some recent studies have shown an association between ABO blood type and pancreatic cancer risk (9, 34), whereas a genome-wide association study (GWAS) comparing patients with pancreatic cancer to controls and subsequent investigations showed a relationship between *ABO* gene locus and pancreatic cancer risk (10–12). Moreover, one hypothesis proposes that the difference in ABO antigens in gastric mucins influences the properties of HP binding, and explains the difference in pancreatic cancer risk among ABO blood types (35). A recent large prospective cohort study identified a statistically significant association between serologic ABO blood type and the risk of GC in a Western population, and suggested that people with blood type A have a higher risk of GC than those with blood type O (4). In our study, we used SNPs at the *ABO* gene locus to assess the impact of *ABO* genotype on the risk of GC. Compared with individuals with the *AA* genotype, only those with *OO* and *BO* genotypes had significantly decreased ORs of 0.70 (CI, 0.50–0.99) and 0.53 (CI, 0.36–0.77), respectively. Risk of GC and AG tended to increase with addition of the *A* allele, whereas that of GC and HP infection tended to decrease with addition of the *B* allele. Although the association between *BB* genotype and GC risk was not statistically significant, this may be because of small number of subjects with *BB* genotype and/or potential factors. From these findings, we suspect that the association between ABO blood type and GC risk may occur through an effect on the differences among *ABO* alleles in AG prevalence and HP infection.

As described by the study of Tatemichi and colleagues, HP infection is a risk factor for both diffuse-type and intestinal-type GC, and the high titer of anti-HP IgG antibody is closely associated with diffuse-type GC (36). They also described that AG with intestinal metaplasia is linked to intestinal-type GC. In our study, the degree of association between ABO blood type and GC risk was different between the 2 histologic types, and there was only a weak association in intestinal type. Although the reason for this difference between 2 histologic subtypes is unclear, the association between ABO blood type and AG risk may be affected by potential factors. Moreover, because associations between ABO blood type and risk of AG and HP infection were inconsistent with previous studies (13, 31, 32), further evaluation should be necessarily to confirm these associations. Nonetheless, our study replicated previous findings regarding ABO blood type and GC risk (4). The mechanism by which genetic variants in the *ABO* gene locus influence the risk of GC, AG, and HP infection has not been fully investigated. The *ABO* gene encodes a glycosyltransferase, and the *A* and *B* alleles encode proteins which differ minimally in amino acid sequence but catalyze the transfer of different carbohydrates (N-acetylgalactosamine or galactose) onto the H antigen to form the A or B antigens (10). In contrast, the *O* allele contains a single base deletion and does not lead to the production of A or B antigens (10). ABO or ABH antigens are expressed on the surface of red blood cells and numerous

other tissues throughout the body (37). Glycoconjugates, such as ABO antigen, are important mediators of intercellular adhesion and membrane signaling, which are both critical to the progression and spread of malignant cells (11, 38). These cell surface molecules are also recognized by the host immune response and may influence immunosurveillance for malignant cells (11, 38, 39). In addition, the activity of the glycosyltransferase, encoded by the *ABO* gene, has been associated with circulating levels of von Willebrand factor and the risk of venous thromboembolism (12, 40). Furthermore, recent GWASs suggest that SNPs at the *ABO* gene locus are associated with several serum markers of inflammation—TNF-α, soluble intercellular adhesion molecule-1 (ICAM-1), soluble E-selectin, and soluble P-selectin (41–45). These findings support the possibility that ABO blood group alleles might correlate with systemic inflammatory state and immune cell recruitment, and thereby influence the risk of several cancers and certain diseases (11, 12, 40, 45). We therefore suspect that the association of *ABO* genotype with the risk of GC, AG, and HP infection results from genetic variations at the *ABO* gene locus and/or genetic variations which are closely linked to the *ABO* gene.

Our study has several methodologic issues which warrant discussion. First, the control population was selected from noncancer patients at ACCH. It is reasonable to assume that these patients are from the same base population from which case subjects were selected, warranting internal validity. With regard to external validity, we previously showed that individuals selected randomly from our control population were similar to the general population of Nagoya City in terms of the exposure of interest (19). Second, blood type was derived from genotype rather than serologic data. Although methods for determining blood type on the basis of a subject's DNA are well established (21, 46, 47), measurement error and exposure misclassification might have occurred. Additionally, the non–deletion-type *O* allele and *cis-AB* allele could not be detected with our method, albeit that these are extremely rare among Japanese (20, 21, 23). Third, we did not assess the HP infection status of GC cases. Given that the advanced gastric atrophy occurring in many patients with GC induces the elimination of HP from the gastric mucosa, measurement of HP does not necessarily reflect current or former infection status (48, 49). A potential limitation was residual confounding by known and unknown risk factors; in particular, the limited number of cases, particularly when stratified by genotype, indicates that our findings need replication in a larger study. Moreover, case–control studies may have suffered from recall bias. Nevertheless, the HERPACC system is less prone to this bias than typical hospital-based studies as the data for all patients are collected before diagnosis. Finally, our study was limited to a Japanese population and the results cannot necessarily be extrapolated to other populations. In summary, our case–control study showed that SNPs at the *ABO* gene locus were associated with the risk of GC in a Japanese population. This finding supports the recently reported association between blood type A and elevated risk of GC (4). Moreover, the *ABO* gene locus may be associated with AG prevalence and HP infection, and these associations may affect the association between ABO blood type and GC risk. Further investigation of these findings in other ethnic groups is warranted, and the mechanism by which the *ABO* gene locus influences the risk of GC, AG, and HP infection should be fully elucidated.

Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank the doctors, nurses, technical staff, and hospital administration staff of Aichi Cancer Center Hospital for their efforts and contribution toward daily management of the HERPACC study. We also thank Dr. Saeko Ogata at the Medico-Legal Section, Criminal Investigation Laboratory, Metropolitan Police Department for her helpful support and comments.

Grant Support

This study was supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan; the Japan Society for the promotion of Science A3 Foresight Program; and research grants from the Aichi Cancer Research Foundation.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 5, 2011; revised April 26, 2011; accepted June 8, 2011; published OnlineFirst June 15, 2011.

References

1. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2003: based on data from 13 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clin Oncol 2009;39:850–8.
2. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006;12:354–62.
3. Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. Methods Mol Biol 2009;472:467–77.
4. Edgren G, Hjalgrim H, Rostgaard K, Norda R, Wikman A, Melbye M, et al. Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. Am J Epidemiol 2010;172:1280–5.
5. Aird I, Bentall HH, Roberts JA. A relationship between cancer of stomach and the ABO blood groups. Br Med J 1953;1:799–801.
6. Lee HH, Wu HY, Chuang YC, Chang AS, Chao HH, Chen KY, et al. Epidemiologic characteristics and multiple risk factors of stomach cancer in Taiwan. Anticancer Res 1990;10:875–81.
7. Fuchs CS, Mayer RJ. Gastric carcinoma. N Engl J Med 1995;333:32–41.
8. El H II, Hashash JG, Baz EM, Abdul-Baki H, Sharara AI. ABO blood group and gastric cancer: rekindling an old fire? South Med J 2007;100:726–7.
9. Iodice S, Maisonneuve P, Botteri E, Sandri MT, Lowenfels AB. ABO blood group and cancer. Eur J Cancer 2010;46:3345–50.

10. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet 2009;41:986–90.
11. Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res 2010;70:1015–23.
12. Wolpin BM, Kraft P, Xu M, Steplowski E, Olsson ML, Arslan AA, et al. Variant ABO blood group alleles, secretor status, and risk of pancreatic cancer: results from the pancreatic cancer cohort consortium. Cancer Epidemiol Biomarkers Prev 2010;19:3140–9.
13. Shibata A, Hamajima N, Ikehara Y, Saito T, Matsuo K, Katsuda N, et al. ABO blood type, Lewis and Secretor genotypes, and chronic atrophic gastritis: a cross-sectional study in Japan. Gastric Cancer 2003;6:8–16.
14. Miwa H, Go MF, Sato NH. pylori and gastric cancer: the Asian enigma. Am J Gastroenterol 2002;97:1106–12.
15. Adamu MA, Weck MN, Gao L, Brenner H. Incidence of chronic atrophic gastritis: systematic review and meta-analysis of follow-up studies. Eur J Epidemiol 2010;25:439–48.
16. Konturek PC, Konturek SJ, Brzozowski T. Helicobacter pylori infection in gastric cancerogenesis. J Physiol Pharmacol 2009;60:3–21.
17. Tajima K, Hirose K, Inoue M, Takezaki T, Hamajima N, Kuroishi T. A model of practical cancer prevention for out-patients visiting a hospital: the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). Asian Pac J Cancer Prev 2000;1:35–47.
18. Hamajima N, Matsuo K, Saito T, Hirose K, Inoue M, Takezaki T, et al. Gene-environment interactions and polymorphism studies of cancer risk in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II). Asian Pac J Cancer Prev 2001;2:99–107.
19. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, et al. Epidemiological features of first-visit outpatients in Japan: comparison with general population and variation by sex, age, and season. J Clin Epidemiol 1997;50:69–77.
20. Suzuki K. ABO blood group alleles and genetic recombination. Leg Med (Tokyo) 2005;7:205–12.
21. Ogata S, Katagiri H, Kobayashi M, Ui H, Yoshii T. An examination by TaqMan PCR method with a specific probe on ABO blood typing. Jpn J Forensic Sci Technol 2007;12:167–76.
22. Nishimukai H, Fukumori Y, Tsujimura R, Okiura T, Tanabe R, Orimoto C, et al. Rare alleles of the ABO blood group system in two European populations. Leg Med (Tokyo). 2009;11 Suppl 1:S479–81.
23. Kobayashi K, Iwasaki M, Anan K, Suzuki Y, Suzuki H, Tamai S, et al. An analysis of polymorphism for ABO blood group genes in a Japanese based on polymerase chain reaction. Anthropological Sci 1999;107: 109–21.
24. Livak KJ. Allelic discrimination using fluorogenic probes and the 5′ nuclease assay. Genet Anal 1999;14:143–9.
25. Inoue M, Kobayashi S, Matsuura A, Hamajima N, Tajima K, Tominaga S. Agreement of endoscopic findings and serum pepsinogen levels as an indicator of atrophic gastritis. Cancer Epidemiol Biomarkers Prev 1998;7:261–3.
26. Fukuda S, Shimoyama T, Umegaki N, Mikami T, Nakano H, Munakata A. Effect of Helicobacter pylori eradication in the treatment of Japanese patients with chronic idiopathic urticaria. J Gastroenterol 2004;39:827–30.
27. Sasazuki S, Inoue M, Iwasaki M, Otani T, Yamamoto S, Ikeda S, et al. Effect of Helicobacter pylori infection combined with CagA and pepsinogen status on gastric cancer development among Japanese men and women: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2006;15:1341–7.
28. Fukumori Y, Ohnoki S, Shibata H, Nishimukai H. Suballeles of the ABO blood group system in a Japanese population. Hum Hered 1996; 46:85–91.
29. Aird I, Lee DR, Roberts JA. ABO blood groups and cancer of oesophagus, cancerof pancreas, and pituitary adenoma. Br Med J 1960;1:1163–6.
30. Vogel F. Controversy in human genetics. ABO blood groups and disease. Am J Hum Genet 1970;22:464–75.
31. Mentis A, Blackwell CC, Weir DM, Spiliadis C, Dailianas A, Skandalis N. ABO blood group, secretor status and detection of Helicobacter pylori among patients with gastric or duodenal ulcers. Epidemiol Infect 1991;106:221–9.
32. Loffeld RJ, Stobberingh E. Helicobacter pylori and ABO blood groups. J Clin Pathol 1991;44:516–7.
33. Boren T, Falk P, Roth KA, Larson G, Normark S. Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. Science. 1993;262:1892–5.
34. Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst 2009;101:424–31.
35. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst 2010;102:502–5.
36. Tatemichi M, Sasazuki S, Inoue M, Tsugane S. Different etiological role of Helicobacter pylori (Hp) infection in carcinogenesis between differentiated and undifferentiated gastric cancers: a nested case-control study using IgG titer against Hp surface antigen. Acta Oncol 2008;47:360–5.
37. Szulman AE. The Histological Distribution of the Blood Group Substances in Man as Disclosed by Immunofluorescence: II. The H Antigen and Its Relation to a and B Antigens. J Exp Med 1962; 115:977–96.
38. Hakomori S. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. Biochim Biophys Acta 1999;1473:247–66.
39. Hakomori S. Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anti-cancer vaccines. Adv Exp Med Biol 2001;491:369–402.
40. Wiggins KL, Smith NL, Glazer NL, Rosendaal FR, Heckbert SR, Psaty BM, et al. ABO genotype and risk of thrombotic events and hemorrhagic stroke. J Thromb Haemost 2009;7:263–9.
41. Barbalic M, Dupuis J, Dehghan A, Bis JC, Hoogeveen RC, Schnabel RB, et al. Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. Hum Mol Genet 2010;19:1863–72.
42. Pare G, Chasman DI, Kellogg M, Zee RY, Rifai N, Badola S, et al. Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women. PLoS Genet 2008;4:e1000118.
43. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet 2008;4:e1000072.
44. Paterson AD, Lopes-Virella MF, Waggott D, Boright AP, Hosseini SM, Carter RE, et al. Genome-wide association identifies the ABO blood group as a major locus associated with serum levels of soluble E-selectin. Arterioscler Thromb Vasc Biol 2009;29:1958–67.
45. Qi L, Cornelis MC, Kraft P, Jensen M, van Dam RM, Sun Q, et al. Genetic variants in ABO blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes. Hum Mol Genet 2010;19: 1856–62.
46. Yip SP. Single-tube multiplex PCR-SSCP analysis distinguishes 7 common ABO alleles and readily identifies new alleles. Blood 2000;95:1487–92.
47. Gassner C, Schmarda A, Nussbaumer W, Schonitzer D. ABO glycosyltransferase genotyping by polymerase chain reaction using sequence-specific primers. Blood 1996;88:1852–6.
48. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, et al. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. Int J Cancer 2004;109:138–43.
49. Matsuo K, Tajima K, Suzuki T, Kawase T, Watanabe M, Shitara K, et al. Association of prostate stem cell antigen gene polymorphisms with the risk of stomach cancer in Japanese. Int J Cancer 2009;125: 1961–4.