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ABO blood group and risk of renal cell cancer

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Abstract

Background—The genetic determinants of sporadic renal cell cancer (RCC) are largely unknown. Previous studies have suggested associations between ABO blood group and risk of various cancers. However, its relationship to RCC remains unclear and no prospective data are available.

Methods—We prospectively followed up 77,242 women in the Nurses' Health Study and 30,071 men in the Health Professionals Follow-Up Study from 1996 to 2008. The information on the ABO blood group was collected from participants' self-reports in 1996. Incidence of pathology-confirmed RCC was compared using hazard ratios (HRs) and 95% confidence intervals (CIs) derived from Cox proportional hazards models.

Results—During 12 years of follow-up, 163 cases of incident RCC were documented in women and 88 cases in men. The multivariate HRs between non-O blood group (combined group of A, AB, and B) vs. blood group O were 1.51 (95% CI 1.09–2.09) in women, 1.08 (95% CI 0.70–1.66) in men, and 1.32 (95% CI 0.95–1.82) in the pooled cohorts. The associations between ABO blood group and RCC were consistent across strata of known risk factors for RCC including age, obesity, smoking, and history of hypertension (*P*interaction 0.32).

Conclusions—We found a suggestive non-significant association between non-O blood group and increased risk of RCC in the pooled cohorts of men and women, and this association was significant in women. Our findings need to be replicated by other prospective studies.

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Author contribution

Hee-Kyung Joh was responsible for the study concept and design, analysis and interpretation of data, and drafting of the manuscript. Eunyoung Cho was responsible for the study concept and design, acquisition and interpretation of data, and critical revision of the manuscript for important intellectual content. Toni K. Choueiri was responsible for the study concept and design, and provided critical revision of the manuscript for important intellectual content.

Responsibility statement

Hee-Kyung Joh and Eunyoung Cho had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

All authors have no relevant conflict of interest to disclose.

Keywords

ABO blood-group system; Blood group antigens; Carcinoma; Renal cell; Kidney neoplasms

1. Introduction

Renal cell cancer (RCC) accounts for 85% cases of kidney cancer, which is the 7th most common cancer among men and the 8th among women in the United States in 2010 [1]. The incidence of RCC has increased worldwide during the past three decades, contributing to a steady rise in mortality rate per unit population [2]. The established RCC risk factors are obesity, smoking, and history of hypertension, and 2–3% of RCC cases are related to familial and autosomal dominant syndromes (e.g., von Hippel–Lindau syndrome). However, most RCC patients have no identifiable risk factors [2], and predisposing genetic factors for RCC remain unclear.

Blood group antigens are common, inherited, and partially penetrant genetic factors, and the ABO blood group was the first blood group antigen system recognized in 1901. The ABO antigens were originally ascribed to erythrocytes, but were later found in numerous other tissues throughout the body, predominantly in endodermal epithelial cells (e.g. oral, gastrointestinal, bronchopulmonary, and urogenital) and several types of parenchymal cells including kidney [3,4]. Blood antigens are now known to be important as receptors or ligands for microbes and immunologically important proteins [5], although the underlying mechanisms are still largely unknown. More recently, mounting evidence revealed the relationship between the ABO blood group and certain malignancies, including cancer of the stomach [6], pancreas [7,8], ovary [9], salivary gland [3], and skin [10]. However, studies on the association between ABO blood group and RCC are sparse, and to our knowledge, no prospective studies have examined the relationship. In this study, we prospectively evaluated the association between the ABO blood group and risk of RCC in two large and independent cohorts of men and women.

2. Methods

2.1. Study population and follow-up

The Nurses' Health Study (NHS) cohort was established in 1976 when 121,700 US female registered nurses aged 30–55 years returned a mailed questionnaire about medical history and various risk factors for chronic disease. The Health Professionals Follow-Up Study (HPFS) began in 1986 when 51,529 US male health professionals (dentists, optometrists, osteopathists, pharmacists, podiatrists, and veterinarians) aged 40–75 years completed a baseline questionnaire on diet, lifestyle, and medical history. In both cohorts, follow-up questionnaires were sent every two years to update information on lifestyle factors and newly diagnosed diseases. Deaths in these cohorts were identified by reports from next of kin and the National Death Index. The follow-up rates are 95.3% in the NHS and 96.4% in the HPFS. These cohorts are described in detail elsewhere [11,12]. The NHS was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA); the HPFS was approved by the Harvard Institutional Review Board.

2.2. Assessment of ABO blood group

On the 1996 questionnaire, participants in both cohorts were asked their blood group (A/B/AB/O, or unknown) and Rh factor (positive/negative, or unknown). Among participants who returned the 1996 questionnaire, 77% of women and 70% of men provided ABO blood group information; among those, 95% of women and 84% of men also reported Rh type [7].

In the validation study based on a subsample of 98 participants from these two cohorts, self-reported ABO blood group was 93% concordant with laboratory-assessed serologic blood group in the NHS and 90% in the HPFS, and concordance rates of Rh type were 100% and 96%, respectively [7]. In the current analysis, we included participants who provided information on the ABO blood group.

2.3. Ascertainment of renal cell cancer

Self-reported information on newly diagnosed kidney cancer was obtained on each biennial questionnaire. Participants (or next of kin on behalf of decedents) who reported a diagnosis of kidney cancer were asked for permission to access their medical and pathological records. Physicians blinded to participants' information reviewed the records. Based on the WHO classification [13], clear cell, papillary, chromophobe, collecting duct carcinoma, and RCC not otherwise classified were included as RCC cases. We excluded individuals who reported any cancer (except for nonmelanoma skin cancer) before baseline and kidney cancer not confirmed by pathology reports.

2.4. Assessment of other risk factors

Information on medical history and lifestyle factors has been updated every two years. Body mass index (BMI, kg/m^2) was calculated using height from baseline and updated body weight. Physician-diagnosed hypertension and diabetes were self-reported and validated in each cohort. For past and current smokers, pack-years of smoking were calculated by multiplying duration and dose of smoking. Parity was reported on the 1996 questionnaire. Alcohol intake during the previous year has been asked every four years using the validated food frequency questionnaire, and cumulative average intake was used in analyses.

2.5. Statistical analysis

Participants were prospectively followed up for the diagnosis of incident RCC from 1996 to 2008. Person-years of follow-up were calculated from the date of return of the 1996 questionnaire to the date of RCC diagnosis, the date of death from any cause, or the end of follow-up, whichever came first.

Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs). The proportionality assumption of Cox models was not violated. In the multivariate models, we adjusted for potential confounders, including age (in month), race (white/non-white), BMI (kg/m^2 , continuous), history of hypertension or diabetes, smoking status (never/past/current) and pack-years (continuous), alcohol consumption (g/day), and parity (in women: nulliparous, 1–2, 3, 4, 5 children).

We examined whether the association between the ABO blood group and risk of RCC varied by the known RCC risk factors: age (<65, 65 years), BMI (<27.5, 27.5 kg/m^2), smoking status (ever, never), and history of hypertension (yes, no). Tests for interaction were performed by the Wald test, using cross-product terms of ABO blood group and stratification variables.

We conducted separate analyses for each cohort, and then pooled the HRs from two cohorts with meta-analytic methods using a random effects model [14]. Statistical tests were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC). All *P* values were 2-tailed; *P* < 0.05 was considered statistically significant.

3. Results

During 12 years of follow-up of 107,313 participants (77,242 women and 30,071 men), we confirmed 251 cases of incident RCC (163 in women and 88 in men). The baseline characteristics of the participants were similar across the four ABO blood groups, and the distributions of blood groups in the NHS and HPFS were similar (Table 1).

The multivariate HRs adjusted for age, race, BMI, history of hypertension or diabetes, smoking status and pack-years, alcohol consumption, and parity (among women) did not differ materially from the age-adjusted HR (Table 2). Compared with women who had blood group O, women with blood group A had a significantly higher risk of RCC (multivariate HR 1.58, 95% CI 1.11–2.26), and women with blood group AB (HR 1.52, 95% CI 0.86–2.70) and B (HR 1.31, 95% CI 0.80–2.14) had non-significantly increased risks. When we combined blood groups of A, AB, and B into non-O blood group, the risk of RCC in non-O blood group was significantly higher than blood group O in women (multivariate HR 1.51, 95% CI 1.09–2.09). In contrast, no significant associations were observed between the ABO blood group and RCC risk in men. The pooled HRs across women and men was 1.32 (95% CI 0.95–1.82) for non-O blood group compared with blood group O. When we restricted analyses to non-Hispanic whites (158 cases in women, 78 cases in men), the multivariate HRs (95% CIs) for non-O blood group were 1.50 (1.08–2.09) in women, 1.18 (0.74–1.88) in men, and 1.38 (1.06–1.81) in the pooled cohorts. Further adjustment for physical activity, fruit and vegetable intakes did not affect the results. Rh factor was not associated with the risk of RCC in either women or men (pooled HR 0.79, 95% CI 0.56–1.11). We observed no effect modifications by Rh factor in the associations between the ABO blood group and RCC risk (data not shown).

The associations between the ABO blood group and RCC risk were consistent across strata of age, BMI, smoking, and history of hypertension in both women and men (*Pinteraction* 0.32) (Table 3).

4. Discussion

In these two independent prospective cohorts of women and men, we found a suggestive non-significant association between non-O blood group and increased risk of RCC in the pooled cohorts, and this association was significant in women.

The ABO antigens are expressed on the surface of erythrocytes and numerous other tissues throughout the body [3]. Recently, various disease associations with the ABO antigens have been demonstrated, including certain malignancies [5]. For instance, non-O blood group was associated with a higher risk of pancreatic cancer [7,8,15] and a lower risk of non-melanoma skin cancer [10]; blood group B was related to a higher risk of ovarian cancer [9].

However, previous epidemiologic studies on the association between the ABO blood group and RCC risk have been sparse and inconsistent. In a clinical case study, the relative frequencies of blood groups of A Rh–, B Rh+, and O Rh– were higher in the 125 RCC cases than in general population in the US [16], while another study in Greece did not observe a significant difference [17]. One case–control study comparing the ABO blood group distributions between 276 kidney cancer patients and controls (patients with other types of cancer) reported no associations between the ABO blood group and kidney cancer [18], but this result could be biased if blood group was associated with non-kidney cancers (the referent group). Since all of the previous studies were retrospective, they were prone to selection bias. None of them evaluated the association by gender.

Several plausible biological links between the ABO blood group and RCC might explain the observed results in our study. First, during renal tumorigenesis, structural changes in ABO antigens have been demonstrated. Malignant cells tend to lose normal ABO antigens [19,20] or acquire new antigens, so-called tumor antigens [21]. The ABO antigens on cell surfaces act as important mediators of intercellular adhesion and membrane signaling which are integral to malignant progression and spread [3,4,7,8]. Thus the cancer-associated ABO antigen changes might have implications for RCC. Second, activated angiogenesis and coagulation cascade might be a possible link. Hypervascularity and hypercoagulability are typical characteristics of RCC and play significant roles in tumor proliferation and metastasis [22]. In the non-O blood group, deletion of A or B antigens induces up-regulation of precursor H and Lewis^y expression, and both precursors exert angiogenic effects [23]. Also, the ABO group is a major determinant of plasma levels of von Willebrand factor (vWF) and factor VIII [24], which are detected in the endothelial cells of RCC [25]. Because non-O blood group individuals have higher levels of vWF and factor VIII, they have a higher risk of venous thromboembolism than blood group O individuals [24]. In a recent genetic analysis, ABO gene locus polymorphisms had effects on plasma levels of these coagulation factors [24]. Third, blood group antigens may be related to systemic inflammation. Chronic inflammation is a predisposition to RCC development [26] and survival [27]. Several recent genome-wide association studies revealed that single nucleotide polymorphisms at the ABO gene locus were significantly associated with the levels of plasma inflammatory markers [15,28].

The disparity across men and women in the associations between ABO blood group and RCC risk is not easily interpretable. As we had the smaller number of cases in men than in women, the null association in men might be due to a limited statistical power (20% for RR = 1.32) to ascertain the association. Alternatively, sex hormones might explain the gender-differential relationships. In a study of gastric adenocarcinoma, blood group A was associated with a significantly higher expression of estrogen and progesterone receptors (androgen receptor was not measured in this study) [29]. But to our knowledge, no prior prospective studies demonstrated gender differences in the relationship between ABO blood group and specific cancer risks [7,10]. In this study, we found no significant effect modifications by age, which may be related to sex hormone levels. To clarify the effects of gender, further studies are needed to investigate the complex relationship between sex hormones and ABO blood group in RCC.

This study has several limitations. First, the ABO blood group was self-reported, but misclassification should be low, since all participants were health professionals whose accuracy of the reports is likely to be high. Also, their accuracy was proven in validation studies with laboratory-assessed serologic blood group [7]. Second, despite a large cohort size, the numbers of RCC cases were limited in some blood groups, especially in men. Third, our study population mainly consisted of white participants, which may limit the generalizability of our results. Further investigations that include other ethnic groups are warranted.

The strengths of this study include a prospective design with high follow-up rates. To our knowledge, this is the first prospective cohort study investigating the relationship between the ABO blood group and RCC risk. We ascertained RCC based on histological evidence to reduce misclassification. We updated information on most of the established risk factors for RCC to reduce residual confounding.

In conclusion, non-O blood group was associated with a higher risk of RCC compared with blood group O in women, but not in men. Our results suggest that the ABO blood group may be a genetically determined predisposing factor of RCC, especially in women. Our findings

need to be replicated by prospective studies in other populations, and further studies that elucidate the underlying biological mechanisms are warranted.

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Age-standardized characteristic of study participants in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) in 1996.^a

Table 1

	NHS				HPFS			
	O	A	AB	B	O	A	AB	B
No. of individuals	33,201	27,478	6142	10,421	12,929	11,127	2306	3709
Percentage of total	43.0	35.6	8.0	13.5	43.0	37.0	7.7	12.3
Age, mean, y	62.2	62.2	62.3	62.2	63.3	63.4	63.5	63.4
White, %	97.4	98.3	96.7	96.4	91.3	91.9	89.2	88.2
Rh factor present, %	76.8	78.7	76.6	77.6	76.6	82.6	73.5	77.9
BMI, mean, kg/m ²	26.7	26.6	26.5	26.7	26.0	26.0	26.0	25.9
Current smokers, %	12.5	12.0	13.5	12.5	5.8	5.7	6.6	6.1
Past smokers, %	43.9	43.4	43.2	43.6	47.5	46.5	47.0	48.4
Pack-years of smoking, ^b mean	24.8	24.4	24.8	24.3	25.4	24.9	25.7	25.1
History of hypertension, %	41.8	40.3	41.4	41.8	2541	24.7	26.1	25.4
History of diabetes, %	7.7	8.0	8.8	8.2	4.7	4.5	6.0	5.0
Alcohol intake, g/d	5.8	5.7	5.9	5.7	11.1	11.0	10.6	10.6
Parity (No. of children), ^c mean	3.0	3.0	3.0	3.0	-	-	-	-

BMI, body mass index.

^aExcept for the data on mean of age, all data are standardized to the age distribution of each cohort.

^bAmong current or past smokers.

^cAmong parous women

Table 2

Age-adjusted and multivariate hazard ratios (95% confidence intervals) of renal cell cancer by ABO blood group and Rh factor in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS), 1996–2008.

	ABO blood group					Rh factor ^a	
	O	A	AB	B	Non-O (A/AB/B)	Positive	Negative
NHS							
No. of cases	55	70	15	23	108	127	30
Person-years	374,360	309,240	68,497	117,283	495,021	642,824	184,404
Age-adjusted HR (95% CI)	1 (ref)	1.55 (1.09–2.21)	1.50 (0.84–2.65)	1.32 (0.81–2.14)	1.49 (1.07–2.06)	1 (ref)	0.83 (0.56–1.24)
Multivariate HR ^b (95% CI)	1 (ref)	1.58 (1.11–2.26)	1.52 (0.86–2.70)	1.31 (0.80–2.14)	1.51 (1.09–2.09)	1 (ref)	0.84 (0.56–1.25)
HPFS							
No. of cases	35	36	5	12	53	65	11
Person-years	136,617	120,592	24,385	40,165	185,143	228,740	58,747
Age-adjusted HR (95% CI)	1 (ref)	1.09 (0.68–1.75)	0.84 (0.33–2.14)	1.16 (0.60–2.25)	1.07 (0.70–1.65)	1 (ref)	0.66 (0.34–1.25)
Multivariate HR ^b (95% CI)	1 (ref)	1.11 (0.69–1.77)	0.80 (0.31–2.07)	1.16 (0.60–2.26)	1.08 (0.70–1.66)	1 (ref)	0.67 (0.35–1.28)
Pooled^c							
Age-adjusted HR (95% CI)	1 (ref)	1.35 (0.96–1.89)	1.27 (0.76–2.12)	1.26 (0.85–1.86)	1.31 (0.96–1.78)	1 (ref)	0.78 (0.55–1.09)
Multivariate HR ^b (95% CI)	1 (ref)	1.37 (0.97–1.94)	1.24 (0.69–2.22)	1.26 (0.85–1.86)	1.32 (0.95–1.82)	1 (ref)	0.79 (0.56–1.11)

HR, hazard ratio; CI, confidence interval.

^aNumbers of person-years and cases do not add up to total due to missing data on Rh factor.

^bAdjusted for age in months, race (white, non-white), body mass index (kg/m², continuous), history of hypertension (yes, no), history of diabetes (yes, no), smoking status (never, past, current), pack-years of smoking (continuous), alcohol intake (g/d), and parity (among women only: nulliparous, 1–2, 3, 4, 5+ children).

^cThe multivariate hazard ratios from each cohort were combined with meta-analytic methods using random effects model.

Table 3

Multivariate hazard ratios (95% confidence intervals)^a of renal cell cancer in stratified analyses.

	NHS		HPFS		Pooled ^c	
	Cases ^b	O	Non-O (A/AB/B)	Cases ^b	O	Non-O (A/AB/B)
Age (year)						
<65	60	1 (ref)	1.42 (0.84–2.43)	28	1 (ref)	1.44 (0.93–2.25)
65	103	1 (ref)	1.54 (1.02–2.32)	60	1 (ref)	1.23 (0.75–2.00)
<i>P</i> interaction ^d			0.85			0.68
BMI (kg/m ²)						
<27.5	84	1 (ref)	1.37 (0.87–2.15)	55	1 (ref)	1.31 (0.92–1.86)
27.5	79	1 (ref)	1.68 (1.04–2.72)	33	1 (ref)	1.40 (0.86–2.27)
<i>P</i> interaction ^d			0.80			0.75
Smoking						
Never	78	1 (ref)	1.59 (0.98–2.56)	39	1 (ref)	1.46 (0.98–2.15)
Ever	85	1 (ref)	1.43 (0.91–2.24)	43	1 (ref)	1.30 (0.90–1.86)
<i>P</i> interaction ^d			0.67			0.54
Hypertension						
No	51	1 (ref)	1.66 (0.91–3.00)	37	1 (ref)	1.42 (0.91–2.24)
Yes	112	1 (ref)	1.42 (0.96–2.09)	51	1 (ref)	1.24 (0.87–1.77)
<i>P</i> interaction ^d			0.71			0.55

NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; BMI, body mass index.

^aMultivariate adjustments include all factors listed in the footnotes in Table 2, excluding the stratification variable.

^bTotal numbers of cases varied due to missing data on the stratification factor.

^cThe multivariate hazard ratios from each cohort were combined with meta-analytic methods using random effects model.

^dBased on the Wald test.