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ABO blood group and risk of epithelial ovarian cancer within the Ovarian Cancer Association Consortium

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Abstract

Purpose—Previous studies have examined the association between ABO blood group and ovarian cancer risk, with inconclusive results.

Methods—In 8 studies participating in the Ovarian Cancer Association Consortium (OCAC), we determined ABO blood groups and diplotypes by genotyping 3 SNPs in the *ABO* locus. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in each study using logistic regression; individual study results were combined using random effects meta-analysis.

Results—Compared to blood group O, the A blood group was associated with a modestly increased ovarian cancer risk: (OR: 1.09; 95% CI: 1.01–1.18; p=0.03). In diplotype analysis, the AO, but not the AA diplotype was associated with increased risk (AO: OR: 1.11; 95% CI: 1.01–1.22; p=0.03; AA: OR: 1.03; 95% CI: 0.87–1.21; p=0.76). Neither AB nor the B blood groups were associated with risk. Results were similar across ovarian cancer histologic subtypes.

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Conflict of Interest
The authors declare that they have no conflict of interest.

Conclusion—Consistent with most previous reports, the A blood type was associated modestly with increased ovarian cancer risk in this large analysis of multiple studies of ovarian cancer. Future studies investigating potential biologic mechanisms are warranted.

Keywords

ovarian cancer; ABO blood group; Ovarian Cancer Association Consortium (OCAC); genetic epidemiology

Introduction

Ovarian cancer is the fifth leading cause of cancer death for women in the U.S. and the seventh most fatal worldwide (1, 2). There are few confirmed risk factors for ovarian cancer and no current strategies for early detection and screening. Thus, the identification of new risk factors for ovarian cancer is critical for developing early detection and screening methods. Several studies of ABO blood group (derived from serologic testing) and ovarian cancer risk, comparing cases to either hospital-based or blood donor controls, suggest increased risk of ovarian cancer with the A blood group compared to the O blood group (3–6). However, a recent analysis using self-reported blood type from the Nurses' Health Study (NHS) reported increased ovarian cancer risk associated with the B allele (i.e. blood types AB or B) (7). To address these inconsistent findings, we imputed ABO blood group using 3 SNPs from the *ABO* locus in 8 studies participating in the Ovarian Cancer Association Consortium (OCAC) and evaluated the associations of ABO blood group (A, AB, B, or O) as well as diplotype (AA, AO, AB, BB, BO, or OO) with risk of ovarian cancer. Further, the A blood group can be divided into two main subtypes: A1 and A2. These subtypes are very similar, except that the A2 allele has a deletion of a single nucleotide, resulting in a frameshift that adds 21 amino acids to the protein product, resulting in diminished enzyme activity (8). Thus we used information from one of the SNPs to separate the A1 and A2 alleles and test whether associations differed between the two alleles. We further investigated whether the associations differ by histologic subtype or between normal weight vs. overweight women, as previously reported in the NHS (7).

Materials and Methods

Study Populations and Genotyping

Details of the 8 studies that participated in this analysis have been published previously (9–11) (Supplemental Table 1). Five population-based case-control studies were included in the analysis: the NCI Ovarian Cancer Case-Control Study in Poland (POL); the Familial Ovarian Tumor Study; Toronto, Ontario (TOR); the North Carolina Ovarian Cancer Study (NCO); the Tampa Bay Ovarian Cancer Study (TBO); and the New England Case-Control Study of Ovarian Cancer (NEC). Additionally, a clinic-based case-control study, Mayo Clinic Ovarian Cancer Case-Control Study (MAY), and a case-control study nested within the Nurses' Health Study (NHS) and NHSII cohorts were included. The eighth study features cases from four studies: the UK SEARCH Ovarian Cancer Study; the United Kingdom Ovarian Cancer Population Study; the Royal Marsden Hospital Ovarian Cancer Study; and the Cancer Research UK Familial Ovarian Cancer Register. Controls were from two sources: the 1958 Birth Cohort; and the Colorectal Tumor Gene Identification consortium. These UK sources will be collectively referred to as UKG.

ABO blood groups were inferred by estimating haplotypes of 2 SNPs in the *ABO* locus. In 60 HapMap phase 2 Caucasians, haplotypes estimated from rs687289 and rs8176746 were perfectly correlated (r^2=1) with the O and B blood types, respectively (12); however rs687289 was not included on the genome-wide association study (GWAS) platforms

utilized by studies included in this analysis. Therefore, we genotyped rs505922, which is in perfect LD with rs687289 in HapMap2 samples. Additionally, we genotyped rs8176704, which distinguishes the A1 from the A2 allele (13). In all studies except NEC and NHS, the *ABO* SNPs were genotyped as part of an ovarian cancer GWAS (14) (Supplemental Table 1). For POL, genotyping was conducted using the Illumina 660W-Quad chip. For TOR, NCO, MAY, TBO and UKG cases, the Illumina 610K chip was used; for UKG controls, the Illumina 550K chip was used; and for NEC and NHS, genotypes were determined using Taqman. For the high-throughput genotyping, the following quality control criteria were met for all three SNPs: 1) no deviation from Hardy-Weinberg equilibrium ($p > 10^{-4}$) and 2) not monomorphic and 3) call rate > 95%. Duplicate concordance was >99.99% for both platforms (14). For the Taqman genotyping, 10% of the samples were run in duplicate. Duplicate concordance was 100% and all 3 SNPs were in Hardy-Weinberg equilibrium.

Statistical Methods

All analyses were restricted to subjects of European background. Blood groups were determined by estimating haplotypes of the three genotyped SNPs. Main analyses were conducted for both blood group (A, AB, B vs. O) and for diplotypes (AA, AO, AB, BB, BO vs. OO). Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using unconditional logistic regression for each study population. Study-specific estimates were combined using random effects meta-analysis. The Q statistic was used to test for heterogeneity between studies. Analyses in each study were adjusted for age, except UKG, which was unadjusted. NEC was additionally adjusted for enrollment phase (1992–1997 or 1998–2002); NHS was additionally adjusted for DNA source (blood vs. cheek) and cohort (NHSI vs. NHSII). As a sensitivity analysis, unadjusted models were run in all studies to assess whether the UKG results might be confounded by age; no differences in association were observed (data not shown). Secondary analyses examined the A1 and A2 alleles separately (information on A1 vs. A2 was not available in UKG), potential differences in association by histologic subtype (serous, mucinous, endometrioid) and potential effect modification by body mass index (BMI) and age. The BMI interaction was tested because the NHS previously reported a stronger ovarian cancer association between blood types B and AB among overweight women compared to women with BMI $<25 kg/m^2$ (7). To test for interactions with BMI and age, we included multiplicative interaction terms between BMI (<25 vs. ≥25) or age (<55 vs. ≥55) and each blood group in each of the individual studies, except the UKG, which did not have information on age and BMI. Subsequently, we meta-analyzed the betas and standard errors for the multiplicative interaction terms and used the p-value for each meta-analyzed interaction term as p-interaction for each blood group-BMI combination.

Results

The distribution of the ABO SNPs was similar across the 8 studies (Table 1). All 3 SNPs were in Hardy-Weinberg equilibrium; the frequencies of the O, A, AB, B blood groups in controls were similar to those reported previously (15, 16). In the combined studies, the A blood group was associated with an increased risk of ovarian cancer (OR: 1.09; 95% CI: 1.01–1.18; p=0.03) compared to the O blood group (Table 2a). However, when examining associations with diplotype, this association was only observed for the A/O, and not the A/A, diplotype (Table 2b). No statistically significant associations were observed for the B (OR: 1.03; 95%CI: 0.88–1.20; p=0.76) or AB (OR: 1.09; 95% CI: 0.89–1.33; p=0.40) blood groups. When the A blood groups were further separated into the A1 and A2 alleles, only the A1 blood group was associated with increased risk of ovarian cancer (A1: OR: 1.15; 95% CI: 1.02–1.30; p=0.03; A2: OR: 1.02; 95% CI: 0.85–1.22; p=0.83; Table 3a). As in the diplotype analysis above, only the A1/O diplotype was associated with increased ovarian

cancer risk (Table 3b). There was no evidence for heterogeneity across studies – p-values for heterogeneity ranged from 0.22 to 0.84.

The associations were similar across the histologic subtypes (Supplemental Table 2), with the possible exception of the AB blood type, which was associated with statistically non-significant increased risk of endometrioid ovarian cancer (OR: 1.39; 95% CI: 0.84–2.30). When stratified by BMI (<25 vs. ≥25 kg/m^2), the increased risk associated with the A blood type was limited to those with BMI ≥ 25 (OR: 1.29; 95% CI: 1.09–1.53) (Supplemental Table 2). However, the interaction was not statistically significant (p=0.08). We found no evidence for an interaction with age (data not shown).

Discussion

In 8 studies participating in the Ovarian Cancer Association Consortium (OCAC), we observed an increased risk of ovarian cancer for the A blood type. In diplotype analysis, this association was only observed in the AO, but not AA diplotype, indicating that this finding may be due to chance. However, the confidence interval for the AA diplotype was wide and the confidence intervals for the AO and AA diplotypes substantially overlapped. Given that the frequency of the AA diplotype was only ~17% among those with blood group A, we may have had low power to detect associations with this diplotype.

Most previous studies have reported increased ovarian cancer risk associated with the A blood group compared to the O group (ORs ranged from 1.17–1.28) (3–6). These studies compared blood group distributions in ovarian cancer cases compared to large groups of controls. However, many of these studies have potential flaws, including the use of male controls, hospital controls, lack of adjustment for potential confounders, such as age and race, and control groups recruited at different times than the case groups, all of which could introduce bias into their results, as discussed in detail by Gates et al (7). Further, because previous studies relied on self-reported or serotyped blood group, they could not assess associations with specific diplotypes; ours is the first study to examine blood group diplotypes in relation to ovarian cancer risk.

In a recent study of self-reported blood type and ovarian cancer risk from the NHS (7), we observed an increased risk of ovarian cancer among women with any B allele (i.e., blood groups B and AB) compared to women with the O blood type (RR=1.41; 95% CI: 1.06–1.88). In the NHS nested case-control study, the concordance between self-reported blood type and genotype-derived blood group was 88%, similar to what has previously been reported (16). However, NHS women tended to over-report the less common blood groups (B and AB; Supplemental Table 3); an additional 40% of NHS women did not know their blood type; these two sources of error combined may have led to a false positive result for types B and AB in the previous analysis in NHS. The previous studies that found increased risk with blood group A had blood group data from serologic testing rather than self-report (3–6); thus the likelihood of misclassified blood groups was much lower in those studies.

The potential mechanisms linking blood group to ovarian cancer risk are unclear. As discussed in the recent manuscript by Gates et al (7), ABO blood type has been linked to immune surveillance, and to blood levels of soluble ICAM-1, tumor necrosis factor alpha, and soluble E-selectin, which are associated with cell adhesion and apoptosis. However, these mechanistic links do not explain why the A blood type would confer ovarian cancer susceptibility. Notably, although ICAM-1 has been associated with ABO blood group in three studies, the A type was associated with lower ICAM-1 levels in two of the three studies (12, 17), which is the opposite result than would be expected if the A blood group is promoting tumor aggressiveness. Further, in the two studies that observed associations

between ABO and E-selectin, the A blood group was associated with lower levels of E-selectin compared to O in one (18) and levels did not differ between the blood groups O and A in the other (19). Thus, it seems unlikely that the association between blood group A and ovarian cancer risk is being driven through altered cellular adhesion and motility. Alternately, it is possible that the *ABO* SNPs genotyped here are in linkage disequilibrium with variation in another genetic locus. Therefore, further research is needed to clarify the biologic mechanisms which link blood group to carcinogenesis.

There are two important limitations in the current study. First, controls in the UKG study were not selected at the same time as the cases and may not represent the population that gave rise to the cases. However, in a sensitivity analysis excluding the UKG study populations, the association with the A blood group was largely unchanged (Supplemental Table 4), suggesting that the UKG controls are not a large source of bias. Second, the current study had limited power for the analysis of subgroups, such as potential differences by histologic type, particularly for the less common types, such as clear cell. However, although not statistically significant within all groups, the results were largely consistent among the three most common histologic types (serous, endometrioid, and mucinous). Further, with 5,233 cases and 6,838 controls, this is the largest study of the association between ABO blood group and ovarian cancer to date, with 80% power to detect a relative risk of 1.17 for the AB blood group, indicating that we had adequate power to detect modest associations with even the rarest blood group. Further, this study improves upon previous studies by using appropriate control groups as well as genotype-derived blood groups, which are less likely to suffer from misclassification compared to self-reported blood type. Additionally, the use of genotype-derived blood groups allowed a more detailed investigation of diplotypes rather than the simple blood groups previously investigated.

In summary, our findings for blood group are consistent with previous findings of increased ovarian cancer risk with blood group A. Although potentially due to chance, the finding that this association is limited to the A1/O diplotype should be confirmed in additional studies. Given that the A blood type is associated with a modest increase in ovarian cancer risk, further research into the biological mechanisms linking blood group with carcinogenesis is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Genotype-derived blood group distributions by case-control status in each participating study.

	Case/control blood group			
Study (N cases/N controls)	**O (%)**	**A (%)**	**B (%)**	**AB (%)**
MAY (357/520)	38/41	48/42	11/12	3/5
NCO (493/650)	44/45	43/43	10/9	3/3
NEC (1031/1051)	42/45	42/41	12/10	4/4
NHS (336/991)	45/43	42/44	9/10	4/2
POL (245/557)	36/34	40/36	15/21	9/9
TBO (225/168)	40/52	46/35	11/9	3/5
TOR (730/555)	45/47	41/39	10/10	4/4
UKG (1816/2345)	43/44	45/44	8/9	3/3
Total (5233/6837)	**42/44**	**44/42**	**10/11**	**4/4**

Table 2

Table 2a ABO blood group and risk of ovarian cancer in 8 studies from the Ovarian Cancer Association Consortium

	MAY[a]	NCO[a]	NEC[b]	NHS[c]	POL[a]	TBO[a]	TOR[a]	UKG[d]	meta-analysis[f]				
Blood group	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**Cases (N)**	**Controls (N)**	**OR**	**(95% CI)**	**p**
O	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2222	2987	**1.00**	(ref.)	
A	1.21	1.04	1.10	0.92	1.03	1.67	1.23	1.07	2286	2865	**1.09**	(1.01–1.18)	**0.03**
B	0.95	1.21	1.26	0.89	0.66	1.59	1.14	0.93	529	732	**1.03**	(0.88–1.20)	0.76
AB	0.78	1.13	1.03	1.48	0.86	0.69	1.28	1.21	195	253	**1.09**	(0.89–1.33)	0.40

Table 2b ABO diplotype and risk of ovarian cancer in 8 studies from the Ovarian Cancer Association Consortium

	MAY[a]	NCO[a]	NEC[b]	NHS[c]	POL[a]	TBO[a]	TOR[a]	UKG[d]	meta-analysis[f]				
Diplotype	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**OR**	**Cases (N)**	**Controls (N)**	**OR**	**(95% CI)**	**p**
O/O	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2222	2987	**1.00**	(ref.)	
A/O	1.35	0.98	1.14	0.95	0.95	1.71	1.26	1.09	1912	2363	**1.11**	(1.01–1.22)	**0.03**
A/A	0.67	1.37	0.93	0.74	1.36	1.58	1.09	0.99	374	502	**1.03**	(0.87–1.21)	0.76
B/O	0.95	1.15	1.23	0.88	0.67	1.69	1.17	0.95	495	681	**1.09**	(0.88–1.19)	0.73
B/B	0.94	2.85	1.76	0.96	0.61	NA[e]	0.89	0.53	34	51	**0.98**	(0.61–1.56)	0.92
A/B	0.78	1.13	1.03	1.48	0.86	0.69	1.28	1.21	195	253	**1.09**	(0.89–1.33)	0.40

[a] Adjusted for age

[b] Adjusted for age and study phase

[c] Adjusted for age, DNA source (blood vs. cheek) and cohort (NHS vs. NHSII)

[d] Unadjusted

[e] There were no cases with the BB diplotype.

[f] Results were combined using random-effects meta-analysis; all p-heterogeneity across studies were >0.20

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Table 3a

ABO blood group incorporating the A2 allele and risk of ovarian cancer in 7 studies from the Ovarian Cancer Association Consortium[a]

Diplotype	Cases (N)	Controls (N)	OR	95% CI	p[b]
O/O	1442	1948	**1.00**	(ref.)	
A1	1108	1356	**1.15**	(1.02–1.30)	**0.03**
A2	269	372	**1.02**	(0.85–1.22)	0.83
A1/A2	86	116	**1.02**	(0.72–1.46)	0.89
A1/B	106	150	**1.02**	(0.78–1.34)	0.88
A2/B	28	36	**1.15**	(0.67–1.96)	0.62
B	377	514	**1.05**	(0.87–1.27)	0.58

[a] UKG was not included in this analysis.

[b] Studies were combined using random effects meta-analysis; all p-heterogeneity between studies >0.20.

Table 3b

ABO diplotypes incorporating the A2 allele and risk of ovarian cancer in 7 studies from the Ovarian Cancer Association Consortium[a]

Diplotype	Cases (N)	Controls (N)	OR	95% CI	p[b]
O/O	1442	1948	**1.00**	(ref.)	
A1/O	955	1155	**1.17**	(1.02–1.33)	**0.02**
A1/A1	153	201	**1.07**	(0.81–1.40)	0.65
A2/O	260	356	**1.03**	(0.86–1.23)	0.76
A2/A2	9	16	**1.10**	(0.43–2.79)	0.85
A1/A2	86	116	**1.03**	(0.72–1.46)	0.89
A1/B	106	150	**1.02**	(0.78–1.34)	0.88
A2/B	28	36	**1.15**	(0.67–1.97)	0.61
B/O	347	473	**1.05**	(0.87–1.27)	0.58
B/B	30	41	**1.10**	(0.66–1.85)	0.71

[a] UKG was not included in this analysis.

[b] Studies were combined using random effects meta-analysis; all p-heterogeneity between studies >0.20.