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ABO blood group and incidence of epithelial ovarian cancer

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Abstract

Previous studies have observed an association between ABO blood group and risk of certain malignancies, including ovarian cancer; however, no prospective studies of the association with ovarian cancer risk are available. Using data from 49,153 women in the Nurses' Health Study, we examined the association between ABO blood group and incidence of epithelial ovarian cancer. Study participants reported their blood type and Rh factor in 1996, and 234 women were diagnosed with incident ovarian cancer during 10 years of follow-up. We used Cox proportional hazards regression to model the incidence rate ratios (RR) and 95% confidence intervals (CI) of ovarian cancer for each blood group category. Compared to women with blood group O, women with blood group AB or B had a non-significant 38% increase in ovarian cancer incidence (95% CI=0.88–2.16 for blood group AB and 0.96–1.99 for blood group B), while blood group A was not associated with risk (RR=0.95, 95% CI=0.70–1.30). Combining blood groups AB and B, we observed a statistically significant positive association with presence versus absence of the B antigen overall (RR=1.41, 95% CI=1.06–1.88) and for the serous invasive subtype (RR=1.53, 95% CI=1.08–2.17). In this large, prospective cohort of women, presence of the B antigen was positively associated with ovarian cancer incidence, while blood group A was not associated with risk. Additional studies are needed to confirm this association and to explore the mechanisms through which blood group may influence ovarian cancer risk.

Keywords

Ovarian Neoplasms; ABO Blood Group; Cohort Studies; Prospective Studies

Novelty and impact

In the first prospective analysis of ABO blood group and ovarian cancer risk, presence of the B blood group antigen was positively associated with ovarian cancer incidence, while blood group A was not associated with risk. Additional research is needed to confirm this

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association and to explore potential mechanisms through which blood group may influence ovarian carcinogenesis.

INTRODUCTION

Previous studies suggest a possible association between ABO blood group and risk of certain malignancies,[1] including an increased risk of ovarian cancer for blood group A versus O;[1–4] however, no prospective studies of the blood group/ovarian cancer association have been published. In a recent analysis of 107,503 men and women in two prospective cohorts, individuals with blood group A, AB, or B had an increased incidence of pancreatic cancer compared to those with blood group O, with the highest risk among those with blood group B.[5] Although the mechanisms for this association are unclear, blood group antigens are expressed on the surface of gastrointestinal, bronchopulmonary, skin, and urogenital epithelial cells,[6] suggesting that blood group may influence carcinogenesis at multiple sites. We therefore examined the association between ABO blood group and incidence of ovarian cancer over 10 years among 49,153 women in the Nurses' Health Study (NHS).

MATERIALS AND METHODS

Study population

The NHS began in 1976 when 121,700 U.S. female registered nurses aged 30–55 completed a mailed questionnaire about known and suspected risk factors for cancer and cardiovascular disease. Participants completed follow-up questionnaires every two years, providing updated information on lifestyle factors and disease diagnoses. The Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital, Boston, MA approved this analysis, and all participants provided implied consent by completing the baseline questionnaire.

In 1996, we asked participants to report their blood type (A, AB, B, O, unknown) and Rh factor (positive, negative, unknown). Seventy-seven percent of respondents provided their blood type, and 95% of these women also provided their Rh type. A validation study comparing reported blood type to serologic testing in a subset of NHS participants observed a concordance of 93% for blood type and 100% for Rh factor.[5] Among women who answered the 1996 questionnaire, we obtained 97.9% of the total possible person-years through June 2006.

We collected data on covariates of interest on one or more questionnaires during follow-up. Height, frequency of genital talc use, and duration of breastfeeding across all pregnancies were reported on a single questionnaire, in 1976, 1982, and 1986, respectively. Questions on parity, oral contraceptive use, tubal ligation, hysterectomy, oophorectomy, menopausal status, postmenopausal hormone (PMH) use, weight, smoking status, lactose intake, and family history of breast/ovarian cancer were included on multiple questionnaires during follow-up. In our analysis, we updated the values for these covariates when new data were available and otherwise carried forward the values from the previous cycle or the last cycle when each covariate was assessed.

Identification of ovarian cancer cases

We collected information about new ovarian cancer diagnoses on each questionnaire. For all reported cases, as well as deaths due to ovarian cancer identified through family members, the U.S. National Death Index, or the U.S. Postal Service, we obtained medical records related to the diagnosis. An estimated 98% of all deaths in the NHS are captured through the

National Death Index.[7, 8] A gynecologic pathologist blinded to exposure status reviewed the medical records to confirm the diagnosis, stage, histologic type/subtype, and invasiveness. Therefore, all cases included in the analysis were epithelial cancers confirmed by medical record review.

Statistical Analysis

We excluded participants who did not complete the 1996 questionnaire (n=20,745) or did not report their blood type (n=23,545). In addition, we excluded women with bilateral oophorectomy (n=18,536), menopause due to pelvic irradiation (n=53), or cancer other than nonmelanoma skin cancer (n=9,668) prior to 1996. Participants accrued person-time from the return date of the 1996 questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (excluding nonmelanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up, June 1, 2006.

We used Cox proportional hazards regression to model the incidence rate ratios (RR) and 95% confidence intervals (CI) of ovarian cancer for each blood group category, compared to blood group O. In addition, we examined the association with Rh factor (Rh negative versus Rh positive) and presence versus absence of the A or B antigen (e.g., blood group AB/B versus O/A). We also evaluated associations with serous invasive/poorly differentiated cancers, but were unable to examine the other histologic subtypes separately due to the limited number of cases.

We evaluated several covariates as potential confounders, including parity, duration of oral contraceptive use, tubal ligation, hysterectomy, duration of breastfeeding, family history of breast or ovarian cancer, smoking status, body mass index (BMI), duration of PMH use, and lactose intake. All estimates were unchanged after controlling for these variables; we therefore adjusted our final models for continuous age in months only.

Using the methods of Kaplan and Meier,[9] we plotted the cumulative incidence of ovarian cancer by blood group, and tested for differences in ovarian cancer-free survival by blood group using the log-rank test. Finally, we assessed whether the association with blood group differed by level of several potential effect modifiers, including age, tubal ligation, oral contraceptive use, smoking history, regular talc use, lactose intake, BMI, and Rh factor. For variables collected on multiple questionnaires, we updated the values over time. In addition, we used BMI from the previous follow-up cycle, to minimize the possibility that preclinical ovarian cancer influenced this variable. We tested for effect modification by modeling interaction terms between each potential modifier of interest and indicator variables for each blood group category, and calculating likelihood ratio tests.

RESULTS

Our analysis included 49,153 women with 438,603 person-years between 1996 and June 2006, and 234 confirmed cases of epithelial ovarian cancer. Of the cases, 152 were serous invasive (65%), 26 were endometrioid (11%), 18 were mucinous (8%), and 38 had other, mixed, or unknown histology (16%).

There were no differences in the baseline characteristics of study participants by blood group (Table 1). Forty-three percent of the women in our analysis reported blood type O, 36% type A, 8% type AB, and 13% type B. This frequency distribution is similar to that reported previously for white, non-Hispanic individuals in the United States.[10]

Compared to women with blood group O, those with blood group AB or B had a non-significant increase in ovarian cancer incidence (RR=1.38, 95% CI=0.88–2.16 and RR=1.38,

95% CI=0.96–1.99, respectively) (Table 2). Blood group A and Rh factor were not associated with risk (RR=0.95, 95% CI=0.70–1.30 for blood group A versus O; RR=1.03, 95% CI=0.75–1.40 for Rh negative versus positive). When we examined the association with presence of at least one A or B blood group allele, women with the B antigen (blood group AB/B) had a statistically significant 41% increase in ovarian cancer incidence (95% CI=1.06–1.88), compared to women without the B antigen (blood group O/A), but there was no association with presence of the A antigen (RR=0.95, 95% CI=0.73–1.23).

The results for the association with blood group AB, B, and AB/B combined were slightly stronger when we restricted the analysis to cases with serous invasive histology (Table 2). However, only the association with presence of the B antigen was statistically significant (RR=1.53, 95% CI=1.08–2.17).

The difference between the cumulative incidence of ovarian cancer over 10 years of follow-up for women with blood group AB or B versus O or A was statistically significant (log-rank P=0.01) (Figure 1). The log-rank test was no longer significant when we examined the four blood groups separately (P=0.09) (results not shown).

The associations did not vary consistently across categories of other risk factors (results not shown). We observed a statistically significant interaction between blood group and BMI<25 versus ≥25 kg/m^2 (P-interaction=0.03; Supplementary Table 1); in stratified analyses, positive associations with blood groups AB and B were present among overweight women (RR=2.43, 95% CI=1.36–4.35; RR=1.84, 95% CI=1.08–3.12 for blood groups AB and B, respectively) but not among women with BMI<25 kg/m^2 (RR=0.66, 95% CI=0.30–1.45; RR=1.10, 95% CI=0.65–1.85 for blood groups AB and B, respectively). However, when we stratified by BMI<30 versus ≥30 kg/m^2 there was no evidence of a stronger positive association among obese women (P-interaction=0.47), although the number of cases with BMI ≥30 kg/m^2 and blood group AB (n=4) or B (n=9) was small.

DISCUSSION

In this large, prospective cohort of women, blood groups AB and B were associated with a borderline significant increased incidence of ovarian cancer. The magnitude of the association was similar for blood group AB and blood group B, suggesting that the B antigen may influence ovarian carcinogenesis. In analyses of presence versus absence of a B allele, we observed a statistically significant increase in incidence of all epithelial cancers and the serous invasive subtype. Although the sample size was limited, the stronger positive associations observed among overweight women should be evaluated in future studies.

Several studies have reported a positive association between blood group A and ovarian cancer risk, but no association with blood group B.[1–4, 11, 12] In four studies, the relative frequency of blood group A versus O was higher in ovarian cancer cases than in a large population sample, with estimates of the relative risk ranging from 1.17 to 1.28.[1–4] Although our results do not rule out a modest positive association with blood group A, similar to that reported previously, there are several possible reasons for the observed differences between our results and those of prior studies. All of the previous studies used retrospective data, most did not adjust for age or other possible confounders, and several studies used controls that may not have been representative of the case population. Although we did not observe any confounding by known or suspected ovarian cancer risk factors in our analysis, there is some evidence that blood group distribution may differ by age,[1, 13] making it a potentially important confounder. Further, a few previous studies used hospital-based control populations, which may not be representative of the blood group distribution in the general population if the conditions leading to hospitalization are associated with

blood group. Changes in the population distribution of BMI over time also may have contributed to the differing study results, if BMI modifies the association with blood group. Finally, it is possible that blood group may influence ovarian cancer survival, which could affect the blood group distribution among cases in a retrospective study if some cases do not survive long enough to be enrolled in the study.

While the mechanism for an association between blood group and ovarian cancer risk is unknown, several possible explanations exist. The *ABO* gene on chromosome 9q34 encodes glycotransferases that catalyze the transfer of nucleotide donor sugars to the H antigen to form the ABO blood group antigens.[14] In addition to their expression on red blood cells, blood group antigens are expressed on the surface of gastrointestinal, bronchopulmonary, skin, and urogenital epithelial cells,[6] including some cells of the ovarian surface epithelium and ovarian inclusion cysts.[15] Modified expression of blood group antigens on cancer cells may influence tumorigenesis by altering glycosyltransferase specificity[5] or increasing cell motility, resistance to apoptosis, and immune escape.[6] Alterations in glycosyltransferase specificity may be particularly important for ovarian cancer, given evidence of the possible role of immunity against the glycoprotein MUC1 in inhibiting ovarian carcinogenesis.[16] Recent studies have reported associations between *ABO* genotype and levels of soluble ICAM-1,[17] tumor necrosis factor-alpha,[18] and soluble E-selectin,[19, 20] further supporting a role of the immune response in the association between blood group and ovarian cancer risk. The observed interaction with BMI also suggests a possible immune-mediated mechanism, as the stronger positive associations with blood groups AB and B among overweight women may be related to higher levels of systemic inflammation in these women.[21] Finally, it is possible that the *ABO* gene may be in linkage disequilibrium with another gene that influences ovarian cancer risk.

The prospective nature of our study greatly reduced the possibility that factors related to blood group influenced which cases were included in the analysis. Additional strengths of our analysis include the large study population, the high follow-up percentage, and the availability of detailed covariate data, which allowed us to examine confounding and effect modification by several exposures of interest. Excluding women with prior cancers may have influenced the blood group distribution of our study population if blood group is associated with these malignancies; however, given the size of our population this is unlikely to have had a large impact on the distribution or associations observed. Although the use of self-reported blood type may have introduced some exposure misclassification, the high concordance between reported blood type and serologic testing in a subset of participants suggests that these health professionals report their blood type with a high degree of accuracy. While the total number of cases in our analysis provided reasonable power, we were unable to examine associations with non-serous histologies; analyses in larger populations would be helpful in determining whether the association differs by histologic subtype. In addition, we were unable to examine differences in ovarian cancer survival by blood group, due to the limited sample size and the unavailability of data to adjust for treatment; this would be interesting to evaluate in future studies.

Our results are suggestive of a possible association between the B blood group antigen and increased risk of ovarian cancer. However, given the conflicting results of previous analyses, additional studies are needed to further explore this association. Studies of potential mechanisms for an association between blood group and ovarian cancer risk also are needed, as these studies may help to elucidate the mechanisms involved in ovarian carcinogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

BMI	body mass index
CI	confidence interval
NHS	Nurses' Health Study
PMH	postmenopausal hormone
RR	incidence rate ratio

References

1. Vogel F. Controversy in human genetics. ABO blood groups and disease. Am J Hum Genet. 1970; 22:464–75. [PubMed: 5432291]

2. Osborne RH, Degeorge FV. The ABO blood groups in neoplastic disease of the ovary. Am J Hum Genet. 1963; 15:380–8. [PubMed: 14097232]

3. Bjorkholm E. Blood group distribution in women with ovarian cancer. Int J Epidemiol. 1984; 13:15–7. [PubMed: 6421759]

4. Henderson J, Seagroatt V, Goldacre M. Ovarian cancer and ABO blood groups. J Epidemiol Community Health. 1993; 47:287–9. [PubMed: 8228763]

5. Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, Giovannucci EL, Fuchs CS. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst. 2009; 101:424–31. [PubMed: 19276450]

6. Le Pendu J, Marionneau S, Cailleau-Thomas A, Rocher J, Le Moullac-Vaidye B, Clement M. ABH and Lewis histo-blood group antigens in cancer. APMIS. 2001; 109:9–31. [PubMed: 11297197]

7. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. Am J Epidemiol. 1994; 140:1016–9. [PubMed: 7985649]

8. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. Am J Epidemiol. 1984; 119:837–9. [PubMed: 6720679]

9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–81.

10. Garratty G, Glynn SA, McEntire R. ABO and Rh(D) phenotype frequencies of different racial/ethnic groups in the United States. Transfusion. 2004; 44:703–6. [PubMed: 15104651]

11. Bjarnason O, Tulinius H. Tumours in Iceland. 9. Malignant tumours of the ovary. A histological classification, epidemiological considerations and survival. Acta Pathol Microbiol Immunol Scand A. 1987; 95:185–92. [PubMed: 3618229]

12. Mori M, Kiyosawa H, Miyake H. Case-control study of ovarian cancer in Japan. Cancer. 1984; 53:2746–52. [PubMed: 6722735]

13. Graves WW. A note on the possible relation of blood groups to age and longevity. Ann Intern Med. 1934; 8:747–51.

14. Yazer MH. What a difference 2 nucleotides make: a short review of ABO genetics. Transfus Med Rev. 2005; 19:200–9. [PubMed: 16010650]

15. Welshinger M, Finstad CL, Venkatraman E, Federici MG, Rubin SC, Lewis JL Jr, Lloyd KO. Expression of A, B, and H blood group antigens in epithelial ovarian cancer: relationship to tumor grade and patient survival. Gynecol Oncol. 1996; 62:106–12. [PubMed: 8690281]

16. Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, Finn OJ. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2005; 14:1125–31. [PubMed: 15894662]

17. Pare G, Chasman DI, Kellogg M, Zee RY, Rifai N, Badola S, Miletich JP, Ridker PM. 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. [PubMed: 18604267]

18. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, Lauretani F, Murray A, Gibbs JR, Paolisso G, Rafiq S, Simon-Sanchez J, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet. 2008; 4:e1000072. [PubMed: 18464913]

19. Paterson AD, Lopes-Virella MF, Waggott D, Boright AP, Hosseini SM, Carter RE, Shen E, Mirea L, Bharaj B, Sun L, Bull SB. 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. [PubMed: 19729612]

20. Qi L, Cornelis MC, Kraft P, Jensen M, van Dam RM, Sun Q, Girman CJ, Laurie CC, Mirel DB, Hunter DJ, Rimm E, Hu FB. Genetic variants in ABO blood group region, plasma soluble E-selectin levels, and risk of type 2 diabetes. Hum Mol Genet. 2010 [Epub ahead of print].

21. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J. 2008; 29:2959–71. [PubMed: 18775919]
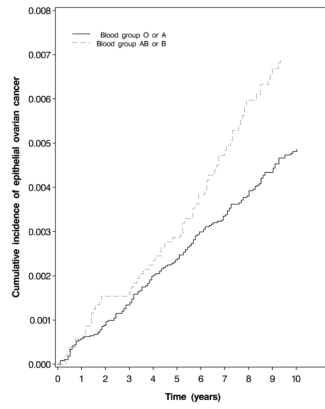
Figure 1.
Cumulative incidence of epithelial ovarian cancer by ABO blood group among 49,153 women in the Nurses' Health Study cohort from 1996 to 2006

Table 1

Baseline characteristics in 1996 by ABO blood group among 49,153 women in the Nurses' Health Study[*]

Characteristic	ABO blood group			
	O	**A**	**AB**	**B**
Number of women	21,167	17,526	3,865	6,595
% of total	43	36	8	13
Mean age in years	62	61	63	61
Rh factor present, %	77	79	77	78
Parous, %	95	96	96	95
Mean parity among parous women	3.2	3.2	3.2	3.2
Ever user of oral contraceptives (OC), %	50	50	49	50
Mean duration of OC use among ever users (months)	51	51	51	51
History of tubal ligation, %	22	22	21	22
Mean body mass index, kg/m^2	26.6	26.6	26.4	26.7
Family history of ovarian cancer, %	3.2	3.1	2.7	3.0

[*]
Standardized by age in six categories (<55, 55–59, 60–64, 65–69, 70–75, ≥75)

Table 2

Age-adjusted incidence rate ratios (RR) and 95% confidence intervals (CI) for the association between ABO blood group and incidence of epithelial ovarian cancer among 49,153 women in the Nurses' Health Study cohort from 1996 to 2006

	Person-years	All epithelial cancers		Serous invasive cancers	
		Cases	RR (95% CI)*	Cases	RR (95% CI)*
ABO blood group					
O	189,414	96	1.00 (referent)	61	1.00 (referent)
A	156,361	73	0.95 (0.70, 1.30)	46	0.94 (0.64, 1.39)
AB	34,228	24	1.38 (0.88, 2.16)	18	1.62 (0.95, 2.75)
B	58,599	41	1.38 (0.96, 1.99)	27	1.42 (0.90, 2.23)
B antigen					
Absent (O/A)	345,776	169	1.00 (referent)	107	1.00 (referent)
Present (B/AB)	92,828	65	1.41 (1.06, 1.88)	45	1.53 (1.08, 2.17)
Rh factor[†]					
Positive	325,177	174	1.00 (referent)	109	1.00 (referent)
Negative	92,701	52	1.03 (0.75, 1.40)	39	1.22 (0.84, 1.76)

*
Adjusted for age in months only; no evidence of confounding by any other covariate examined

[†]
Numbers of person-years and cases do not add up to total due to missing data on Rh factor