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Original Article

ABO blood type is associated with endometrial cancer risk in Chinese women

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Abstract

ABO blood type has been associated with risk of several malignancies. However, results are not consistent. In this population-based case-control study including 1204 incident endometrial cancer cases and 1212 population controls, we examined the association of self-reported serologic blood type with endometrial cancer risk using a logistic regression model. Women with endometrial cancer were more likely to have blood type A. Compared to women with blood type O, the adjusted odds ratios for endometrial cancer were 1.00 [95% confidence interval (CI), 0.79–1.28] for type B, 1.24 (95% CI, 0.90–1.69) for type AB, and 1.50 (95% CI, 1.19–1.90) for type A. A significant dose-response relationship was observed for cancer risk and level of antigen A (*P* for trend = 0.0003). The positive association of blood type A with cancer risk was observed regardless of menopausal status, body mass index, oral contraceptive use, or family cancer history. Our results suggest that ABO blood type may be involved in the development of endometrial cancer.

Key words ABO blood type, endometrial cancer, case-control study

Since Aird *et al.*[1] first reported an association between blood type A and gastric cancer in 1953, numerous reports have documented a high incidence of cancers of the stomach[2], pancreas[3], gallbladder[4], lung[5], kidney[6], breast[7,8], ovaries[9], and uterus[10] for blood type A or B, suggesting a role for inherited human blood group antigens in the development of cancer. Recently, Amundadottir *et al.*[11] conducted a genome-wide association study (PanScan) and identified significant associations of the ABO gene locus with the risk of pancreatic cancer, sparking a new wave of interest in the role of ABO blood types in the development of cancer. More recently, Wolpin *et al.*[12] observed a significantly elevated risk for incident pancreatic cancer among participants with blood types A or B compared to those with blood type O. This result was subsequently confirmed in 1534 cases and 1583 controls from 12 prospective cohorts in PanScan[13]. The association of ABO blood type with gastric cancer[14], breast cancer[15], and skin cancer[16] has also been investigated in recent years, but the results have been inconsistent. In this study, we evaluated the association of blood types with endometrial cancer risk using data from the Shanghai Endometrial Cancer Study, a large population-based case-control study conducted in urban Shanghai, China[17].

Materials and Methods

Study subjects

Using the population-based Shanghai Cancer Registry, we identified 1 449 eligible endometrial cancer case subjects, ranging in age from 30 to 69, who were diagnosed with the malignancy between 1997 and 2003. Cancer diagnosis was confirmed by review of medical records and available pathologic slides. A total of 1204 case subjects completed in-person interviews and were included in this study.

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Control subjects were randomly selected from the general population of Shanghai using the Shanghai Resident Registry, and were matched to cases according to the age distribution of endometrial cancer cases in 1996. Women with a history of cancer or hysterectomy were excluded. Of the 1629 eligible women contacted, 1212 (74.4%) participated in the study. The study protocols were approved by the Institutional Review Boards of all institutes involved in the study, and written informed consent was obtained from all participants prior to participation in the study.

Data collection

Study participants were interviewed in person by trained, retired medical professionals. A structured questionnaire was used to elicit detailed information on serologic blood types (A, AB, B, O, unknown), demographic factors, menstrual and reproductive history, hormone use, prior disease history, dietary habits, physical activity, tobacco and alcohol use, body weight, and family history of cancer. Anthropometrics (weight, height, and waist and hip circumferences) were also taken during the interview using a standard protocol.

Statistical analyses

Chi-square (χ^2) test or *t* test were used to evaluate case-control differences in demographic and lifestyle characteristics. χ^2 test or ANOVA test was used to compare the characteristics among the four blood type groups. The risk of endometrial cancer associated with blood types was estimated by odds ratios (ORs) and 95% confidence intervals (CIs) derived from unconditional logistic regression with adjustment for age and potential confounders. All statistical tests were applied using SAS software (version 9.1) and were based on two-tailed probability.

Results

The descriptive characteristics of cases and controls are shown in Table 1. There were no significant case-control differences with regard to age and hormone replacement therapy (all $P > 0.05$). However, compared with controls, case subjects were more likely to have higher education, history of diabetes mellitus, more cumulative years of menstruation, fewer pregnancies, higher body mass index (BMI), and positive family history of cancer. In addition, case subjects were less likely to exercise, drink alcohol, or use oral contraceptives.

The frequencies of blood types O, B, AB, and A were 36.6%, 25.7%, 12.0%, and 25.7%, respectively, among our control participants. Due to lack of related

Table 1. Comparison of endometrial cancer cases and controls on demographic characteristics and selected risk factors, Shanghai Endometrial Cancer Study, 1997–2003

Factor	Cases (*n* = 1204)	Controls (*n* = 1212)	*P*
Median age (25th, 75th percentile)	54.3(48.5, 62.1)	54.5(48.5, 62.6)	0.77
Education level (%)			
No formal education	7.9	11.0	
Elementary	14.1	13.0	
Junior high school	37.0	36.4	
High school	25.8	26.9	
Post-high school/College	15.1	12.8	0.05
Physical activity in METs (mean ± SD)	10.5±7.3	11.0±4.6	0.05
Oral contraceptive use (%)	18.5	24.9	<0.01
Cancer history among first-degree relatives (%)	35.2	27.9	<0.01
Nulliparous (%)	7.4	3.6	<0.01
No. of pregnancies (mean ± SD)	2.6±1.5	2.9±1.5	<0.01
BMI (kg/m^2) (mean ± SD)	25.7±4.2	23.8±3.5	<0.01
Alcohol consumption (%)	2.8	5.4	<0.01
History of diabetes (%)	15.3	6.9	<0.01
Time of menstruation (years, mean ± SD)	32.8±4.9	30.6±5.4	<0.01
Menopause (%)	58.3	63.1	0.01
Use of HRT (%)	4.4	4.0	0.66

MET, metabolic equivalent; SD, standard deviation; BMI, body mass index; HRT, hormone replacement therapy. Missing values have been excluded. *P* value for *t* test (continuous variables) or χ^2 test (categorical variables).

data from the general population in Shanghai, we compared the frequency distribution of ABO blood types in our control group with that from blood donors in Shanghai [18] and the controls in the Shanghai Breast Cancer Study (SBCS), a large-scale population-based case-control study conducted in Shanghai between 1996 and 1998 [19]. The frequency distribution of ABO blood types in our control group was significantly different from that in blood donors (P for χ^2 test = 0.002) but did not differ from that in the SBCS control group (P for χ^2 test = 0.34) (Table 2).

The characteristics of control participants according to self-reported ABO blood types are presented in Table 3. Women with different ABO blood types were comparable in educational level, postmenopausal status, time of menstruation, number of pregnancies, family history of cancer, history of diabetes, cigarette smoking, alcohol drinking, and BMI. However, a significant difference existed for average age, use of hormone replacement therapy, and use of oral contraceptives.

As shown in Table 4, women with endometrial cancer were more likely than controls to have blood type A. Given that the individuals with blood type O have neither A nor B antigens on the surface of their red cells, the women with the blood type were used as reference in the study. Adjusted OR was 1.50 (95% CI = 1.19–1.90) for blood type A as compared with blood type O. A moderately increased but not statistically significant risk was observed for women with blood type AB compared with women with blood type O (OR = 1.24, 95% CI = 0.90–1.69). These positive associations were observed regardless of menopausal status, BMI, oral contraceptive use, or family cancer history. Blood type B was not associated with the risk of endometrial cancer in our study.

Discussion

Our results provide further evidence that ABO blood

Table 2. Comparison of self-reported ABO blood type frequency among control participants with that among blood donors and the controls of Shanghai Breast Cancer Study (SBCS)

Blood type	Number of subjects (%)		
	Controls in this study	Blood donors[a]	Controls in SBCS
A	252 (25.7)	507 (29.9)	343 (27.8)
B	252 (25.7)	485 (28.6)	323 (26.2)
O	358 (36.6)	517 (30.5)	417 (33.8)
AB	117 (12.0)	186 (11.0)	152 (12.3)

[a]Data from reference [18]. P_1 = 0.002 for comparison between controls in this study and blood donors; P_2 = 0.34 for comparison between two control groups.

Table 3. Characteristics by self-reported ABO blood type among control participants, Shanghai Endometrial Cancer Study, 1997–2003

Characteristic	ABO blood type				P
	O (n = 358)	B (n = 252)	AB (n = 117)	A (n = 252)	
Median age (25th, 75th percentile)	55.1(49.4, 63.4)	54.1(48.7, 60.2)	54.3(49.0, 62.1)	53.5(48.0, 60.9)	0.04
Education of college or above (%)	25.5	30.3	31.9	28.8	0.45
Postmenopausal status (%)	66.8	61.5	65.8	58.7	0.19
Time of menstruation (years, mean ± SD)	30.8±5.5	31.3±4.4	31.3±4.7	30.1±6.0	0.22
No. of pregnancies (mean ± SD)	2.9±1.4	2.6±1.3	2.9±1.3	2.7±1.3	0.09
Family history of cancer (%)	25.5	30.3	31.9	28.8	
History of diabetes (%)	8.1	6.4	4.3	7.5	
Use of HRT (%)	3.4	2.8	5.1	7.5	
Use of oral contraceptives (%)	29.1	25.4	16.2	24.6	
Cigarette smoking (%)	2.5	2.0	5.1	4.8	
Alcohol drinking (%)	5.3	4.0	8.6	5.6	
BMI (mean ± SD)	23.7±3.5	24.2±3.4	23.7±3.4	23.7±3.6	

P value for ANOVA test (continuous variables) or χ^2 test (categorical variables).

Table 4. Association of blood type with endometrial cancer risk, Shanghai Endometrial Cancer Study, 1997–2003[a]

Characteristic	Blood type				*P*
	A	B	AB	A	
All subjects					
Cases/controls	323/358	265/252	126/117	355/252	$P_x^2 = 0.001$
OR (95% CI)					
Age-adjusted	1.00	1.17(0.93–1.47)	1.19(0.89–1.60)	1.56(1.25–1.95)	$P_{trend} < 0.0001$
Fully adjusted[b]	1.00	1.00(0.79–1.28)	1.24(0.90–1.69)	1.50(1.19–1.90)	$P_{trend} = 0.0003$
Menopausal status					
Premenopausal women					
Cases/controls	125/119	113/97	62/40	148/104	$P_x^2 = 0.24$
OR (95% CI)					
Age-adjusted	1.00	1.10(0.76–1.59)	1.53(0.95–2.45)	1.36(0.95–1.94)	$P_{trend} = 0.05$
Fully adjusted[c]	1.00	0.96(0.64–1.44)	1.75(1.04–2.93)	1.39(0.94–2.06)	$P_{trend} = 0.03$
Postmenopausal women					
Cases/controls	198/239	152/155	64/77	207/148	$P_x^2 = 0.0019$
OR (95% CI)					
Age-adjusted	1.00	1.19(0.89–1.59)	1.00(0.69–1.47)	1.69(1.27–2.24)	$P_{trend} = 0.0007$
Fully adjusted[c]	1.00	1.02(0.75–1.39)	0.99(0.66–1.48)	1.64(1.21–2.22)	$P_{trend} = 0.0019$
Body mass index					
BMI<25					
Cases/controls	161/243	107/154	62/78	185/169	$P_x^2 = 0.0037$
OR (95% CI)					
Age-adjusted	1.00	1.05(0.76–1.44)	1.19(0.81–1.76)	1.65(1.24–2.20)	$P_{trend} = 0.0005$
Fully adjusted[c]	1.00	0.99(0.71–1.37)	1.23(0.82–1.85)	1.62(1.20–2.19)	$P_{trend} = 0.0009$
BMI ⩾25					
Cases/controls	157/115	158/98	64/39	167/81	$P_x^2 = 0.16$
OR (95% CI)					
Age-adjusted	1.00	1.15(0.81–1.63)	1.20(0.76–1.92)	1.47(1.03–2.11)	$P_{trend} = 0.04$
Fully adjusted[c]	1.00	1.05(0.73–1.52)	1.11(0.68–1.82)	1.41(0.96–2.07)	$P_{trend} = 0.08$
Oral contraceptive use					
Never					
Cases/controls	256/254	212/188	105/98	298/190	$P_x^2 = 0.0041$
OR (95% CI)					
Age-adjusted	1.00	1.12(0.86–1.46)	1.07(0.77–1.49)	1.57(1.22–2.01)	$P_{trend} = 0.0008$
Fully adjusted[c]	1.00	0.97(0.73–1.29)	1.11(0.79–1.57)	1.49(1.14–1.95)	$P_{trend} = 0.0022$
Ever					
Cases/controls	67/104	53/64	21/19	57/62	$P_x^2 = 0.31$
OR (95% CI)					
Age-adjusted	1.00	1.15(0.71–1.88)	1.62(0.80–3.30)	1.29(0.80–2.10)	$P_{trend} = 0.23$
Fully adjusted[c]	1.00	1.08(0.63–1.83)	2.00(0.91–4.37)	1.47(0.86–2.50)	$P_{trend} = 0.09$
Family history of cancer					
Yes					
Cases/controls	114/90	94/76	36/37	127/72	$P_x^2 = 0.12$
OR (95% CI)					
Age-adjusted	1.00	0.98(0.65–1.47)	0.76(0.45–1.31)	1.40(0.94–2.08)	$P_{trend} = 0.14$
Fully adjusted[c]	1.00	0.90(0.58–1.40)	0.82(0.46–1.46)	1.44(0.93–2.23)	$P_{trend} = 0.11$
No					
Cases/controls	207/263	170/175	89/79	225/178	$P_x^2 = 0.0051$
OR (95% CI)					
Age-adjusted	1.00	1.24(0.94–1.64)	1.44(1.01–2.05)	1.61(1.23–2.11)	$P_{trend} = 0.0004$
Fully adjusted[c]	1.00	1.08(0.80–1.46)	1.56(1.07–2.29)	1.53(1.15–2.05)	$P_{trend} = 0.0012$

[a]A total of 363 missing values were excluded from the analysis. [b]Adjusted for age, education level, menopausal status, time of menstruation, number of pregnancies, oral contraceptive use, hormone replacement therapy, cigarette smoking, alcohol drinking, family history of cancer, diagnosis of diabetes, and body mass index. [c]Similar to b but excluding the corresponding stratified variable.

type may be involved in carcinogenesis. Our finding that women with blood type A had the highest risk for cancers is consistent with some previous studies[1-7,9,10], including a study on uterine cancer[10]; however, this result is inconsistent with several others[6,8,12] that indicated blood type B was linked to the highest risk of cancers.

Several potential mechanisms for the association of the ABO blood type with cancer risk have been proposed, including inflammation, immune surveillance for malignant cells, intercellular adhesion, and membrane signaling[12]. More importantly, blood group antigens are expressed not only on the surface of red blood cells but also on the surface of many other epithelial cells. Alterations in glycosyltransferase specificity may lead to differential expression of blood group antigens on epithelial cells and thus influence tumorigenesis[12]. For endometrial cancer, A, B, and/or H (the precursor of A and B antigens) antigens were reported to be detected in tumors, but no distinct localization of these antigens was observed in normal endometria. H antigen was particularly frequently detected in endometrial cancers[20]. This may help to explain the excess risk of cancer for women with non-O blood types compared to women with blood type O, but it cannot explain the specific role of blood type A. Hence, whether and how antigens A and B function in different ways remains unclear. Interestingly, in this study, the cancer risk increased with increasing level of antigen A, though the number of women with homozygous blood type A in this population was unknown. The dose-response relationship strongly suggests the effect of antigen A in the development of endometrial cancer among Chinese women.

Strengths of this study include the population-based case-control study design, a large sample size, and a relatively high participation rate (82.7% for cases and 74.4% for controls). However, the blood types were self-reported in this study, and there were 363 participants unaware of their blood type. This raised our concern on recall bias and possible selection bias. In this study, the distribution of ABO blood types among controls was significantly different from that obtained from blood donors in Shanghai[18], but did not differ from that in controls of SBCS. Considering that the blood donors were not a randomized sample of general population and no significant difference in distribution of ABO blood types was observed between breast cancer cases and controls in SBCS (P for χ^2 test = 0.19), it is unlikely that our positive results were caused by selection bias. In addition, although age, use of hormone replacement therapy, and use of oral contraceptives differed among the four blood groups in controls, the association of ABO blood types with cancer risk remained unchanged after adjusting for these factors and was consistently observed in subgroups stratified by these factors.

In summary, our study lends further support to the hypothesis that ABO blood type may be a marker of cancer susceptibility. The mechanisms underlying the moderate discrepancy in blood type-cancer associations for different cancers warrant further research.

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