Acta Clin Croat 2021; 60:354-360
doi: 10.20471/acc.2021.60.03.03

Original Scientific Paper

ABO BLOOD GROUP GENOTYPES IN WOMEN WITH BREAST CANCER

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SUMMARY – ABO blood group is a risk factor for several cancers, but it is not clear yet whether the risk of breast cancer is greater in particular ABO blood type carriers. The aim of this case-control study was to examine the correlation between ABO blood group genotypes, estrogen receptor (ER), progesterone receptor (PR) and HER2 status as tumor grade markers (I-III), and the occurrence of breast cancer. The research included 59 patients with invasive breast cancer and 80 asymptomatic, healthy women, blood donors. Genomic DNA was isolated using QIAampDNA Blood Mini Kit (QIAGEN, Germany). Genotyping was performed using in-house polymerase chain reaction with sequence-specific primers (PCR-SSP) method. Comparison of genotypes and phenotypes of ABO blood groups between patients and control group yielded $p>0.05$. There was no statistical significance of correlation between ABO genotypes/phenotypes in either patient group or control group. Testing the significance of different tumor grade occurrence, and ER, PR and HER2/neu status showed no statistical significance in the occurrence of a particular tumor grade, or in ER, PR and HER2/neu status as tumor markers in O1A1 genotype compared to non-O1A1 genotypes. Our study results confirmed that there was no correlation between ABO blood type genotypes/phenotypes and breast cancer in study groups.

Key words: *ABO blood groups; Breast cancer; ABO genotypes; ABO phenotypes*

Introduction

The ABO system is the most important blood group system in transfusion and transplant medicine. The ABO gene located on chromosome 9q34 encodes glycosyltransferase enzymes that add specific sugars to the oligosaccharide chains of H antigens, forming ABO antigens[1]. There are some undoubted associations between ABO blood groups and disease. ABO antigens located on the erythrocyte surface but also presented in various human cells and tissues participate in the pathophysiology of a wide range of diseases, the most important of which are cardiovascular disorders, infectious and tumor diseases[2-4]. Numerous studies have sought to explain the biological basis of the impact of ABO antigen on tumor initiation, survival and spread[5-7]. It is important to emphasize that ABO blood group genotypes correlate significantly with the risk of particular cancers, but they do not cause cancer, only indicating the possibility of its occurrence[8].

Breast cancer is the most common cancer in women in Croatia and accounts for a quarter of newly diagnosed cancers in women[9]. With regular screening that includes self-examination, mammography and ultrasound, breast cancer can be detected at an early stage,

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Received March 25, 2020, accepted October 5, 2020

when the chances of cure and survival are much higher. It most commonly occurs over the age of 50, but can also occur in young women[10]. It is a malignant, epithelial tumor most commonly produced by monoclonal proliferation of terminal duct epithelium or ductal-lobular units of the breast. They are classified into adenocarcinoma groups and are divided into invasive and non-invasive forms[11]. Steroid hormone receptors, estrogen (ER) and progesterone (PR) receptors located in the cell nucleus, and the HER2/neu receptor are predictive factors in hormone therapy response. For cancers expressing ER or PR with more than 75% of positive cancer cells, hormone therapy is the preferred method of treatment[12].

Research on the role and impact of ABO blood groups on the risk and prognosis in breast cancer pathology has yielded contradictory results. Earlier studies conducted in the USA found no correlation[13]. Studies in the populations of Greece and Iceland have shown that women carrying blood type A are more prone to develop neoplasms with poorer prognosis and more aggressive course of the disease. These women represent a significant proportion of breast cancer patients, higher than the current proportion of female carriers of blood group A among the female population[14,15]. On the other hand, women carrying blood group O have some kind of 'protection' from developing breast cancer, and if they develop it, the prognosis is usually more favorable. Women carriers of AB blood groups have similar prognoses as those with blood group A, and women with blood group B having similar prognosis as those with O blood group[16]. In patients with breast cancers and those with metastasis, loss of ABO antigen expression was found, which was a marker of tumor invasiveness but was not significantly associated with HER2 status or prognosis[17].

The aim of this case-control study was to examine the association between ABO blood group genotypes and the occurrence of breast cancers in women from the Croatian population, and to examine the association between ABO genotypes and tumor grade (I-III), ER/PR and HER2 status.

Subjects and Methods

Patient group included 59 women diagnosed with invasive breast cancer, aged 34-82. The patients provided their informed signed consent for scientific research prior to initiating the study. Sampling was performed at the Department of Transfusion Medicine and Coagulation of Oncology Patients, Sestre milosrdnice University Hospital Centre, Zagreb. Control group consisted of 80 asymptomatic and healthy women, nonremunarated blood donors aged 21-70. The study was conducted at the Croatian Institute of Transfusion Medicine (CITM) in Zagreb. The study was approved by the Ethics Committees of the Sestre milosrdnice University Hospital Centre and CITM. Blood samples were collected with K_2EDTA, and genomic DNA was isolated from whole blood using a commercially QIAampDNA Blood Mini Kit (QIAGEN, Hilden, Germany). ABO blood group genotypes were determined by in-house polymerase chain reaction with sequence-specific primers (PCR-SSP) method in 8 parallel PCR-SSP reactions which amplify ABO gene fragment of exons 6 and 7, according to Gassner *et al.* with some modifications[18], with minor changes in primer dilution and PCR amplification conditions. Using this genotyping method, it is possible to distinguish five main ABO alleles: O1, O2, A1, A2, B, and 15 different ABO genotypes. The amplified PCR products were separated by gel electrophoresis.

Statistical analysis

Using the methods of descriptive statistics, the data obtained were expressed according to age of the patient and control groups. The normality of data distribution was examined by D'Agostino-Pearson statistical test. The level of statistical significance of the association of ABO genotypes between the patient group and control group was determined by Fisher exact test. The odds ratio (OR) was determined as a measure of the correlation of data in the contingency table. The OR calculation was used to evaluate the impact of ABO genotypes on the development of breast cancer. The χ^2-test was used to compare the significance of difference in tumor grade (I-III) representation and the status of ER, PR, and HER2 markers between the O1A1 genotype and non-O1A1 genotypes. Due to the small number of samples with some less frequently represented genotypes, data were divided and examined according to the O1A1 genotype, which was most prevalent in patients compared to the non-O1A1 genotypes. Statistical data analysis was performed by use of the MedCalc v. 10.1.2 program (MedCalc Software, Mariakerke, Belgium).

Results

The study involved 59 patients with invasive breast cancer, median age 60.0, and 80 asymptomatic and healthy blood donors, median age 43.5. The data obtained showed that the patient group was significantly older than the control group. Data distribution was tested by D'Agostino-Pearson statistical test. Testing showed that distribution of data on age coincided with normal distribution in the patient group, whereas the respective data distribution differed significantly from normal distribution in the control group ($p<0.05$).

Some ABO genotypes were not present in the patient group (O2A1, BB), others were not present in the control group (O1O2, A2B), and some were not present in either study group (O2O2, O2A2, A2A2, O2B) (Table 1). Statistical analysis of categorical data on patients and controls by Fisher exact test did not establish statistically significant association between ABO genotypes and breast cancer. Table 2 shows OR with 95% confidence interval (95% CI). Comparison of ABO phenotypes in breast cancer patients and control group by Fisher exact test did not establish statistically significant correlation between phenotypes of ABO blood groups and breast cancer (Table 3).

Table 1. Frequency of ABO genotypes in breast cancer patients and control group

ABO phenotype	ABO genotype	Patients N=59 (%)	Controls N=80 (%)
O	O1O1	14 (23.7)	18 (22.5)
	O1O2	2 (3.4)	0
	O2O2	0	0
A	O1A1	21 (35.6)	26 (32.5)
	O1A2	5 (8.5)	4 (5.0)
	O2A2	0	0
	O2A1	0	1 (1.3)
	A1A1	1 (1.7)	5 (6.2)
	A1A2	1 (1.7)	2 (2.5)
	A2A2	0	0
B	O1B	10 (16.9)	17 (21.2)
	O2B	0	0
	BB	0	1 (1.3)
AB	A1B	4 (6.8)	6 (7.5)
	A2B	1 (1.7)	0

Table 2. Comparison of ABO genotypes between patients and control group

ABO genotype	Patients N=59	Controls N=78	OR (95% CI)	p (Fisher)
O1O1	14	18	1.07 (0.48-2.38)	1.000
O1O2	2	0	7.00 (0.33-148.58)	0.179
O1A1	21	26	1.15 (0.57-2.33)	0.720
O1A2	5	4	1.76 (0.45-6.86)	0.495
A1A1	1	5	0.26 (0.03-2.28)	0.241
A1A2	1	2	0.67 (0.06-7.60)	1.000
O1B	10	17	0.76 (0.32-1.80)	0.665
A1B	4	6	0.90 (0.24-3.33)	1.000
A2B	1	0	4.13 (0.17-103.15)	0.424

OR = odds ratio; 95% CI = 95% confidence interval; Fisher = Fisher exact test

Table 3. Comparison of ABO phenotypes between patients and controls

ABO phenotype	Patients N=59	Controls N=80	OR (95% CI)	p (Fisher)
O	16	18	1.28 (0.59-2.79)	0.555
A	28	38	1.00 (0.51-1.96)	1.00
B	10	18	0.70 (0.30-1.66)	0.523
AB	5	6	1.14 (0.33-3.94)	1.00

OR = odds ratio; 95% CI = 95% confidence interval; Fisher = Fisher exact test

Tumor grade, ER, PR and HER2/neu receptor expression status were known for all 59 study patients. For statistical analysis, data on ER and PR status were grouped, so that status 0 indicated patients negative for receptors, status 1 borderline positive, and status 2

Table 4. Comparison of difference in tumor grade, ER, PR and HER2/neu status between O1A1 genotype carriers and non-O1A1 genotype carriers

ABO genotype	Tumor grade			ER status			PR status			HER2/neu status	
	I	II	III	0	1	2	0	1	2	negative	positive
O1A1	2	12	7	2	0	19	6	1	14	18	3
non-O1A1	3	22	13	6	2	30	9	3	26	35	3
Total N=59 (%)	5 (8.5)	34 (57.6)	20 (33.9)	8 (13.6)	2 (3.4)	49 (83.1)	15 (25.4)	4 (6.8)	40 (67.8)	53 (89.8)	6 (10.2)

ER = estrogen receptors; PR = progesterone receptors

receptor positive patients with receptor status 2+ and 3+. For HER2/neu, patients with receptor status 0 and 1+ were considered as negative patients, and those with receptor status 2+ and 3+ as positive ones. Most patients had tumor grade II, ER 2+ status, PR 2+ status, and HER2 negative status. Comparison of difference in tumor grade incidence in O1A1 genotype carriers *versus* non-O1A1 genotypes yielded values of χ^2=0.047 and p=0.977, i.e. there was no statistically significant difference in tumor grade incidence between the O1A1 genotype and non-O1A1 genotypes. Comparing differences in the ER (χ^2=1.713, p=0.425), PR (χ^2=0.329, p=0.848) and HER2/neu (χ^2=0.107, p=0.743) status also showed that there was no statistical significance among the data examined (Table 4).

Discussion

Studies on the association of ABO blood system as a genetic factor for the development of breast cancer conducted to date have not clearly established that the risk correlates with a specific ABO type. The studies by Dede *et al.* including 565 women in Turkey and by Yu *et al.* including 468 patients in the USA did not find correlation between the risk of breast cancer and carrying a specific ABO blood group[19,20]. On the other hand, two Greek studies, first one in 2009 on 166 women[14] and second one 10 years later on 202 women[21], showed antigen A to be associated with a high risk of breast cancer development. The study by Tryggvadottir *et al.* from Iceland conducted on 184 breast cancers inherited in families and 572 sporadic cases showed the risk of disease to be statistically significant for B blood group carriers[15]. In their study on a population of 442 women in Morocco, Zouine *et al.* report on a high incidence of breast cancers in B blood group women[22].

A previous retrospective study on the association of ABO phenotypes and Rh factors and breast cancers in Croatia, conducted in 407 women at the Sestre milosrdnice University Hospital Centre, found no statistically significant difference. The authors found mild, statistically significant correlation between Rh factor and HER2 /neu, which needs to be confirmed in a larger study[23].

The present case-control study involved 59 patients diagnosed with invasive breast cancers and 80 healthy blood donors as a control group. Patient age was found to coincide with normal distribution (p=0.713), while the age of control subjects differed from normal distribution (p=0.049). Complete comparison of the two study groups by age was statistically unreliable due to their age difference. Voluntary blood donors as representatives of a healthy population can donate blood in the age range of 18-65 years, while patient group had no age limit. Comparison of ABO genotypes of patients and control subjects showed that there was no statistical significance between the study groups according to ABO blood group genotypes and occurrence of breast cancer. A limitation of our study was a small number of patients participating in the study, which could have weakened strength of our statistical conclusion. Detection of ABO genotypes allows better resolution of the influence of individual ABO alleles on the correlation examined. However, comparison of ABO phenotypes *versus* breast cancer occurrence in our patients did not result in a statistically significant association.

The results of the study, albeit in a small number of subjects, are consistent with the results of the study by Gates *et al.* in a large sample of 67697 patients and 3107 controls in the USA. They did not find any correlation between ABO genotypes and the risk of inva-

sive, ductal, or ER/PR positive breast cancers[24]. The most recent work by Momenimovahed and Salehiniya dedicated to epidemiological characteristics of and risk factors for breast cancer worldwide also indicates that data on ABO blood groups and risk of developing breast cancer are controversial and many scientists could not confirm this connection[25]. In contrast, a meta-analysis by Miao *et al*. offered a more accurate assessment of the risk by evaluating 14 different studies including 9665 patients and found no association between ABO blood groups and breast cancers. They found blood group A to have a slightly higher risk of breast cancers, with an OR 1.066 and 95% CI 1.001-1.134, only in the Caucasian population[26]. A meta-analysis of 70 different studies by Meo *et al*. from 2017 showed the highest incidence of breast cancer to be reported in A blood group carriers and lowest in AB carriers[27]. Another meta-analysis by Zhang *et al*. included 11 European studies; OR for A *versus* non-A groups was 1.12 (95% CI: 1.01-1.24) and OR for O *versus* non-O was 0.90 (95% CI: 0.85-0.95), suggesting an increased risk of breast tumor in A blood group carriers compared to O blood group carriers[28]. A Scandinavian study by Vasan *et al*. carried out on 1.6 million blood donors with >119,000 cancers at 13 different tumor locations showed a statistically significant association of breast cancer with A and AB blood groups[29]. Discrepancy of the results from different studies are primarily due to differences in the frequency of ABO blood groups between and within populations, study design, in particular size of patient samples, selection of appropriate control group, and methods of determining ABO blood groups[30].

In the study by Klimant *et al*. in the USA, analysis of the association of breast tumor markers HER2/neu, ER and PR status with blood type showed no statistically significant association[31]. This is consistent with our results, which, although in a small number of subjects, did not show statistical significance when compared with the significance of the difference in ER, PR, and HER2/neu status in carriers of the O1A1 genotype *versus* non-O1A1 genotypes either. The results of a recent study by Akin and Altundag showed that the type, grade, stage, and hormonal status of breast cancers did not show significant association with ABO blood groups, which is also consistent with the results of our study[32].

Although the results of many studies did not confirm the association between ABO genotypes and the occurrence of breast cancers, research of the association will certainly continue to arouse interest of scientists and clinicians. Blood group antigens are known to alter the body's response to systemic inflammation. The ABO locus correlates with the concentration of ICAM-1, interstitial adhesion molecules. Glycosylation can affect the clearance rate of SP-selectins and other adhesion proteins. The structures of glycosyltransferases and the role of ABH antigens in inflammatory adhesion processes are indisputable[33,34]. It is important to emphasize that ABO antigens are not only exposed to erythrocytes but also to other vascular endothelial cells and epithelial cells. Protein-receptor interactions and their mutations and recombination in glycosylation could lead to conformational changes in important proteins such as epidermal growth factor receptors, or changes in the recognition of 'foreign cells' by natural killer cells, all contributing to tumorigenesis. In addition, glycosyltransferases are important mediators in membrane signaling and are thought to play a role in malignant tumor progression because they participate in immune control of malignant cells[27,30].

Conclusion

The results of the present case-control study in the group of patients with breast cancers and group of healthy controls showed no statistically significant association. This is consistent with the results of most studies in Caucasian populations, which did not demonstrate an increased risk of developing breast cancers in carriers of a particular ABO phenotype or genotype. Comparison of the significance of difference in tumor grade (I-III) status, ER, PR and HER2/neu receptor markers in O1A1 genotype carriers *versus* non-O1A1 genotype carriers did not show statistical significance. Breast cancer is a multifactorial disease and further studies of other disease markers conducted in a larger number of subjects are needed.

Acknowledgment

The authors are thankful to all colleagues having contributed to this study.

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Sažetak

GENOTIPOVI ABO SUSTAVA KRVNIH GRUPA KOD ŽENA OBOLJELIH OD TUMORA DOJKE

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ABO sustav krvnih grupa povezan je s rizikom od nekih tumorskih bolesti, ali još uvijek nije razjašnjeno je li rizik od tumora dojke veći kod nositeljica određene ABO krvne grupe. Cilj istraživanja bio je ispitati povezanost između genotipova ABO krvnih grupa, zastupljenosti gradusa tumora (I-III) te biljega ER, PR i HER2/neu i razvoja tumora dojke. Istraživanjem je obuhvaćeno 59 bolesnica s invazivnim tumorom dojke i 80 zdravih žena, dobrovoljnih darivateljica krvi. Genomska DNA izolirana je pomoću komercijalnog testnog paketa QIAampDNA Blood Mini Kit (QIAGEN, Njemačka). Genotipizacija uzoraka izvedena je pomoću *in-house* PCR-SSP metode. Usporedbom genotipova i fenotipova ABO krvne grupe između bolesnica i kontrolne skupine dobiven je p>0,05 te nije bilo statističke značajnosti za povezanost ABO genotipova/fenotipova između skupine bolesnica s tumorom dojke i kontrolne skupine. Ispitivanjem značajnosti razlike zastupljenosti gradusa tumora, statusa ER, PR i HER2/neu nisu dobivene statistički značajne vrijednosti za pojavu određenog gradusa tumora te statusa biljega ER, PR i HER2/neu kod genotipa O1A1 u odnosu na genotipove ne-O1A1. Rezultati studije potvrdili su da ne postoji povezanost između genotipova/fenotipova ABO krvnih grupa i tumora dojke kod ispitivanih skupina.

Ključne riječi: *ABO krvne grupe; Tumor dojke; ABO genotipovi; ABO fenotipovi*