ARTICLE Libri Oncol., Vol. 39 (2011), No 1-3, 15 – 19

ASSOCIATION BETWEEN ABO BLOOD GROUP, RH FACTOR AND BREAST CANCER IN PATIENTS TREATED AT THE UNIVERSITY HOSPITAL FOR TUMORS, ZAGREB, CROATIA

MARIJA SKOKO, IRENA MIHIĆ LASAN, JELENA CULEJ, TIHA VUČEMILO and DEANA ŠTURM

Department of Transfusion Medicine, University Hospital for Tumors, "Sestre milosrdnice" University Hospital Center, Zagreb, Croatia

Summary

The study is a retrospective review of 407 female patients with primary breast cancer and 320 female patients with benign breast changes who were surgically treated in the University Hospital for Tumors during calendar year 2009. We investigated a possible link between the ABO blood group and breast cancer. All patients had their blood group (ABO antigen and RhD) determined, as a part of preoperative treatment, at the Department for Transfusion Medicine of the University Hospital for Tumors. Erythrocyte antigens were determined using the plate and microcard technique. The mean age of all patients was 62.1 years (range 30 – 95 yrs). No statistically significant differences were found between patients who have cancer and those who have not in the frequency of certain blood groups (χ = 2.525, df = 3, p = 0.471). Also, there was no statistically significant difference between patients with cancer and those without cancer in the frequency of Rh (χ = 2.343, df = 1, p = 0.076). We found a statistically significant but slight correlation between Rh factor and HER2/neu (p=0.038), r=0.106. According to the correlation coefficient, the correlation between these two variables is none or slight. The causal relationship between the two parameters remains unknown and should be tested in a larger study.

KEYWORDS: *ABO blood groups, Rh factor, breast cancer, HER2/neu*

POVEZANOST ABO KRVNE GRUPE, RH FAKTORA I RAKA DOJKE U BOLESNIKA LIJEČENIH U KLINICI ZA TUMORE

Sažetak

Ispitivanje je retrospektivno obuhvatilo 407 bolesnica s primarnim rakom dojke i 320 bolesnica s dobroćudnim promjenama u dojci koje su kirurški liječene u Klinici za tumore u 2009. godini. Proučavali smo moguću povezanost između ABO krvne grupe i raka dojke. Krvna grupa (ABO antigen i RhD) utvrđena je svim bolesnicama u okviru prijeoperacijske obrade u Službi za transfuzijsku medicinu Klinike za tumore. Antigeni na površini eritrocita određivani su na pločama i u mikrokarticama. Prosječna dob bolesnica iznosila je 62,1 godina (raspon 30 – 95 godina). S obzirom na učestalost određenih krvnih grupa nisu utvrđene statistički značajne razlike između bolesnica koje imaju rak i onih koje ga nemaju (χ = 2,525, df = 3, p = 0,471). Statističkih značajnih razlika u učestalosti Rh faktora između bolesnica s rakom i onih koje ga nemaju, također, nije bilo (χ = 2,343, df = 1, p = 0,076). Otkrivena je statistički znakovita, iako slaba korelaciju između Rh faktora i HER2/neu (p=0,038), r=0,106. Prema koeficijentu korelacije između te dvije varijable korelacije ili nema ili je slaba. Uzročna povezanost između ta dva parametra i dalje je nepoznata i treba je ispitati na većem uzorku.

KLJUČNE RIJEČI: *ABO krvne grupe, Rh faktor, rak dojke, HER2/neu*

INTRODUCTION

Although the ABO blood group antigens are considered to be antigens of erythrocytes, they can actually be found on a diverse palette of human tissue and are present on most epithelial and endothelial cells. Every human RBC has around 2 million ABO antigens. Other blood cells such as T cells, B cells and platelets have ABO antigens which are absorbed from plasma. In people who are secretors, ABO antigens can be found in all body fluids, except in the cerebral spinal fluid (1). The occurrence of any disease could not be linked to them, but a link between susceptibility to a disease and antigen deficiency has been noticed. Such correlations are controversial and need more research. Correlations between blood groups of the ABO system and cancer have been documented since 1921 (2). It has been noticed that people with blood types B and AB are more likely to develop cancer. Individuals with the blood type A are considered more likely to develop stomach cancer (3), while those with type O blood are more likely to get an ulcer (4). Breast cancer is the most common cancer in the female population, representing 27 percent of all cancer diagnoses. Breast cancer must be viewed as a disease which depends on the interactions of numerous external and internal factors. The role of the ABO/Rh blood group as an indicator for breast cancer has been studied in the past but the data had a small prognostic value (5). The aim of this paper is to show this possible link on a group of patients treated in the University Hospital for Tumors during calendar year 2009.

MATERIALS AND METHODS

The study is a retrospective review of 407 female patients with primary breast cancer and 320 female patients with benign breast changes who were surgically treated in the University Hospital for Tumors in 2009. All patients had their blood group (ABO antigen and RhD) determined at the Department for Transfusion Medicine as a part of their preoperative treatment.

Erythrocyte antigens were determined using the plate and microcard technique (erythrocyte agglutination with specific antibodies on dextran molecules soaked in buffer) (6).

The presence of A and B antigens on erythrocytes was determined using a specific serum antibody test: anti-A and anti-B (polyclonal or monoclonal), and the presence of antibodies in the serum using test erythrocytes. The D Antigen was also determined on plates and in microcards. All patients underwent radical or conservative breast surgery. After surgery, the material obtained was processed using standard histopathological methods including fixation of the resection material in 10% buffered formalin, paraffin embedding of tissue specimens, tissue sectioning in 5 μm slices and staining with hemalaun-eosin. The slides were examined by light microscopy to determine tumor grade, and assess axillary lymph node status. HER-2 protein expression was assessed using the HercepTest. For the control group we used data from 320 women who were treated at the same hospital for benign breast changes. All the results were processed using descriptive statistical methods. The χ^2- test was used to test the differences between the groups. A value of $P< 0.05$ was considered as statistically significant. To assess the correlation between ABO blood groups, Rh factor and other prognostic factors for breast cancer correlation analysis was employed. Statistical analysis was performed with SPSS 17.0 software.

RESULTS

Data on 407 women with breast cancer and 320 women with benign tumors (control group) and recorded ABO blood groups were taken for analysis. The mean age of all patients was 62.1 years (range 30 – 95 yrs). The most common type of breast cancer was ductal carcinoma (n=342). The tumor size ranged from 0.2 to 13 cm: 211 (51.8%) patients had a tumor diameter less than or equal to 2 cm, and in 193 (47.4%) tumors were greater than 2 cm in diameter. There were 49 (12%) patients with well differentiated tumor (grade I), 193 (47.4%) patients with moderately differentiated tumor (grade II) and 151 (37.1%) patients with poorly differentiated tumor (grade III). Metastatic nodal disease was present in 203 patients. Table 1 shows baseline patient characteristics.

Figures 1 and 2 show distribution of the ABO blood group and Rh factor among patients and controls.

The distribution of the ABO blood groups and Rh factor among patients, controls and gen-

Table 1.

BASELINE CHARACTERISTICS

Patient characteristics	No. of patients (%) (N=407)
Age (years)	62.1 ± 12.8
Type of cancer	
CDI	342 (84%)
others	65 (16%)
Histological grade	
I	49 (12%)
II	193 (47.4%)
III	151 (37.1%)
missing	14 (3.4%)
Tumor size	
<2	211 (52.2%)
>2	193 (47.8%)
missing	0
Lymph node status	
positive	194 (47.7%)
negative	203 (49.9%)
missing	10 (2.5%)
Her2/neu status	
positive	170 (41.8%)
negative	214 (52.6%)
missing	23 (5.7%)

eral population in Croatia is similar. Data for distribution of the ABO blood groups in the general population were collected from the Croatian Institute for Transfusion Medicine (Table 2).

No statistically significant differences in the frequency of certain blood groups (χ = 2.525, df = 3, p = 0.471) were found between patients with cancer and those without cancer. The control and experimental group did not differ in the prevalence of certain blood group. Also, there was no statistically significant difference between patients who have cancer and those who do not have cancer in the frequency of Rh (χ = 2.343, df = 1, p = 0.076). The control and experimental groups did not differ in the incidence of certain Rh factor. The correlation of blood groups to tumor diameter (p=0.848), type of cancer (p=0.965), HER2/neu status (p=0.960) and lymph node status (p=0.597) was not statistically significant. There was also no statistically significant correlation of the Rh factor to tumor diameter (p=0.079), type of cancer (p=0.866) and lymph node status (p=0.729), but we found a statistically significant although slight correlation between the Rh factor and HER2/neu (p=0.038), r=0.106.

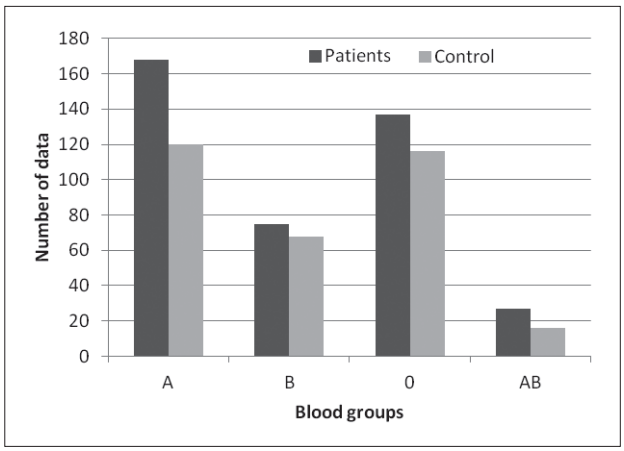

Figure 1. ABO blood type distribution among patients and controls

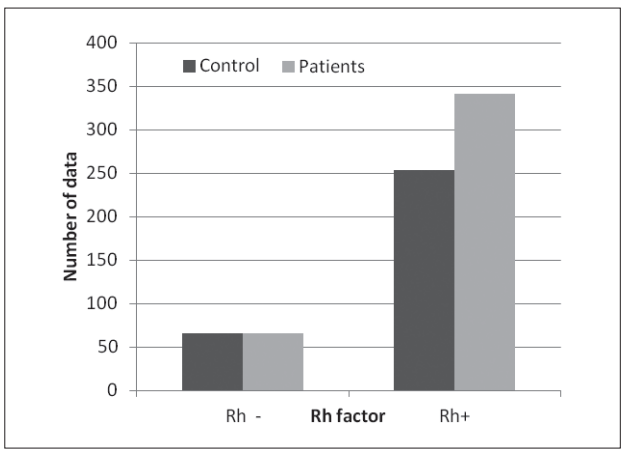

Figure 2. Rh factor status among patients and controls

Table 2.

DISTRIBUTION OF ABO BLOOD GROUPS AND RH FACTOR AMONG PATIENTS, CONTROLS AND GENERAL POPULATION IN CROATIA SHOWN AS A PERCENTAGE.

Blood groups	Patients %	Control %	General population %
A	41.3	37.5	42
B	18.4	21.2	17
A	6.6	5	7
0	33.7	36.2	34
Rh+	84	79.4	85
Rh-	16	20.6	15

DISCUSSION

The role of genetic factors in the development of cancer is widely accepted. During the last two decades, the role of inheritance in breast tumorigenesis has been clearly established, mainly after the description of BRCA1/2 and other genes. In 1921, Alexander noticed and reported that patients with the blood groups B and AB were more susceptible to develop malignancy which can be more aggressive (2). The human ABO gene on chromosome 9 has three common variants of the gene. Different variants are called alleles. The A allele encodes *N*-acetylaminogalactosyltransferase and this enzyme makes the A antigen that confers blood type A. The B allele encodes a variant enzyme that makes the B antigen and gives rise to the blood type B. The O allele encodes a defective enzyme that does not make either antigen (7). These are the basic genetic findings that can explain the role of the ABO blood groups in tumorigenesis. The association of a particular ABO locus on chromosome 9q34 has been identified only for pancreatic cancer (8). Aird and al. discovered a significant correlation between the blood group A and gastric cancer (9). Pandey et al. showed an increased frequency of carcinoma of the gallbladder in blood groups A and AB (10). Anderson and Haas reported a significant excess of blood group A among women with a familial history of breast cancer compared to patients with no familial history (11). Breast cancer patients with blood type AB had the highest rates for pre-menopausal and lymph node negative status, although not statistically significant. Patients with blood type AB had the best outcomes. Onitilo et al. reported that patients who were triple negative had the worst outcomes (12). In our study there was no statistically significant difference between ABO blood group distribution among patients and controls ($p=0.471$). Stamatakos et al. investigated the correlation between breast cancer in Greek women and ABO blood groups. The study was performed on 166 women with breast cancer. Three hundred women with benign breast diseases were used as a control group. They showed that the ductal type occurs more frequently in Rh+ patients regardless to the ABO blood group. In Rh+ patients, ductal breast cancer is commonly observed in patients with the blood group A. The group A, especially the Rh- group A was associated with a worse prognosis (13). They also did not find statistically significant differences between ABO blood group distribution among these two groups. We could not confirm any significant correlation between the type of cancer and Rh positivity ($p=0.866$), but we found a statistically significant but slight positive correlation between the Rh factor and HER2/neu regardless of the ABO blood group. Klimant et al. also studied blood type distribution among 426 breast cancer patients. The distribution did not vary significantly from that of the regional population ($p=0.08$). Patients with blood types A and B had the highest rate of tumors smaller than 2 cm compared to patients who were the blood type AB or O ($p<0.01$). Just like our study, their study also found no statistically significant difference in distribution relative to HER2/neu status. They did not have any data on the Rh status (14). HER2/neu positivity is a result of altered glycosylation, just like loss of ABO expression in tissue. So it is logical to compare these two variables in many researches. It is known that over-expression of HER2 cell membrane receptor protein is associated with tumor cell growth, aggressive disease and shortened survival. In our study, we found a positive correlation between HER2 and the Rh status. According to the Pearson's correlation coefficient, the correlation between these two variables is none or slight. The causal relationship between these two parameters remains unknown and should be tested in a larger study.

CONCLUSION

ABO blood group and Rh factor distribution did not show any statistically significant difference between the two studied groups including patients with breast cancer and patients with benign breast changes. The distribution of blood groups in relation to tumor diameter, type of cancer, HER2/neu status and lymph node status was not statistically significant. We found a statistically significant correlation between the Rh factor and HER2/neu positivity of cancer cells.

REFERENCES

1. Reid ME and Lomas-Francis C. The Blood Group Antigen Facts Book. Second ed. 2004, New York: Elsevier Academic Press.

2. Alexander W. An inquiry into distribution of the blood groups in patients suffering malignant disease**.** Brit J Exp Path 1921; 2: 66
3. Fuchs CS, Mayer RJ. Gastric carcinoma. N Engl J Med 1995; 333: 32-41
4. Reid ME, Bird GW. Associations between human red cell blood group antigens and disease. Transfus Med Rev 1990; 4: 47-55
5. Costantini M, Fassio T, Canobbio L, Landucci M, Resasco M, Boccardo F. Role of blood groups as prognostic factors in primary breast cancer**.** Oncology 1990; 47(**4**)**:** 308-12
6. Lapierre Y. The gel test: A new approach for detection of red cell antibodies/antigen in a solid phase. Proceedings of XX Congress of the International Society of Blood Tranfusion Society. Manchester: British Blood Transfusion Society, 1988: 145
7. Daniels G. Human blood groups, ed 2. Blackwell Science, Malden, MA, 2002
8. Amundadottir L, Kraft P, Stolzenberg-Soloman R Z, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet 2009; 41(9): 986-90
9. Aird I, Bentall HH, Roberts JA. A relationship between cancer of the stomach and the ABO blood groups. Br Med J 1953; 4814: 799-801
10. Pandey M, Gautam A, Shukla VK. ABO and Rh blood groups in patients with cholelithiasis and carcinoma of the gallbladder. BMJ 1995; 310:1639
11. Anderson DE, Haas C. Blood type A and familial breast cancer. Cancer 1984; 54: 1845-9
12. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2/neu expression: comparison of clinicopathologic features and survival. Clin Med Res 2009; 7: 4-13
13. Samatakos M, Kontzoglou K, Safioleas P, Safioleas C, Manti C, Safioleas M. Breast cancer incidence in Greek women in relation to ABO blood groups and Rh factor. Int Semin Surg Oncol 2009; 6: 14
14. Klimant E, Glurich I, Mukesh B, Adedayo A. Blood type, hormone receptor status, HER2/neu status, and survival in breast cancer: A retrospective study exploring relationships in a phenotypically well-defined cohort. Clin Med Res 2011; 9 (3/4): 111-8

Author's address: Marija Skoko, M.D., 'Sestre milosrdnice' University Hospital Center, University Hospital for Tumors, Department of Transfusion Medicine, Ilica 197, 10 000 Zagreb, Croatia; e-mail: skomar.11@gmail.com