

Received: 2018.02.13
Accepted: 2018.03.01
Published: 2018.07.07

Clinical Associations with ABO Blood Group and Rhesus Blood Group Status in Patients with Breast Cancer: A Nationwide Retrospective Study of 3,944 Breast Cancer Patients in Turkey

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 **Serkan Akin**
ACE 2 **Kadri Altundag**

1 Department of Medical Oncology, Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey
2 MKA Breast Cancer Clinic, Tepe Prime, Ankara, Turkey

Corresponding Author: Serkan Akin, e-mail: drserkanakin@gmail.com
Source of support: None

Background: The aim of this study was to investigate the association between A, B, O, Rhesus (Rh)-positive and Rh-negative blood groups and breast cancer in a nationwide cohort of 3,944 patients in Turkey.





Material/Methods: A retrospective study included 3,944 patients diagnosed with breast cancer between 2004 and 2015 and with known blood type. Clinical and demographic patient data included age, sex, body mass index (BMI), menopausal status. The breast tumor type, size, grade, TNM stage, and the presence of lymph node and distant metastases were noted. Histopathology of the breast tumors had included routine detection of human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) levels.

Results: The 3,944 patients with breast cancer were blood group, type A, B, O, and Rh-positive or Rh-negative; the median age was 47.9 years (range, 18.2–89.6 years); 99.5% (3923/3,844) were women, and 0.5% (21/3944) were men. Patients with blood type O had a significantly smaller tumor size compared with patients with blood types A or B. There were no significant differences between blood groups and patient age, BMI, menopausal status, tumor histology, ER status, HER2 status, lymph node and distant metastasis. However, there was a significant difference in the prevalence of lobular breast cancer, levels of ER-positive tumor cells, and prevalence of cases with tumor metastases in Rh-positive patients compared with Rh-negative patients.

Conclusions: The findings of this retrospective study showed that the type, grade, stage, and hormonal status of breast cancer showed no significant associations with ABO blood grouping.

MeSH Keywords: **ABO Blood-Group System • Breast Neoplasms • Rh-Hr Blood-Group System**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/909499>

 1922  2  —  16



Background

The ABO blood group antigens are expressed on the red blood cell membrane and the surface of other normal and pathological cells. Recently, there has been increasing research interest in the association between ABO blood group antigens and the association between certain types of human cancer, particularly with the risk of developing gastric and pancreatic and gastric cancer [1–4]. Recent studies also have shown an association between ABO blood group and hemostasis, thrombosis, cardiovascular disease, as well as other cancer types [2].

Worldwide, breast cancer is the most common malignancy in women, and there are known risk factors that are associated with breast cancer, including female sex, older age, family history, and molecular and gene associations. Although it is now known that the risk of a diffusely infiltrating type of stomach cancer is 20% higher in people with blood type A compared with people with blood type O, the association between blood groups and breast cancer risk and prognosis remains controversial [3]. Recent meta-analysis data has indicated that blood group A conferred an increased risk for developing breast cancer [4,5]. However, because there are conflicting results about the association between ABO blood groups and breast cancer, the associations remain unclear [4,5]. There are also several studies that suggest blood group has prognostic significance in breast cancer [6–10]. One study from Greece showed that individuals with blood group type A and who were also Rhesus (Rh)-negative were more likely to develop metastases following a diagnosis of breast cancer [11]. However, another study reported that patients with breast cancer with blood group type B or AB had poor survival and an increased risk of breast cancer recurrence [10].

The aim of this study was to investigate the association between A, B, O, Rh-positive, and Rh-negative blood groups in a nationwide cohort of 3,944 patients diagnosed with breast cancer between 2004 and 2015 in Turkey.

Material and Methods

A nationwide retrospective review showed that between 2004 and 2015 in Turkey, a total of 4,691 patients were diagnosed with breast cancer, of which 3,944 patients with breast cancer had information on their blood group, type A, B, O, and Rhesus (Rh)-positive or Rh-negative.

Of these patients, hospital records or self-reports provided clinical data that were retrospectively collected for analysis. Clinical data included patient age, menopausal status, blood type A, B, O, and Rh-positive or Rh-negative status. The histopathological data on the breast cancer included the cancer

type (ductal, lobular, or other), the grade, the tumor stage, the presence of lymph node metastases or distant metastases. ABO blood group data were also obtained, from healthy individuals with no known malignancy, from the Turkish Red Crescent to compare with the patient population.

Statistical analysis

All data were analyzed using the SPSS version 16.0 software package (IBM, Chicago, IL, USA). Frequency distributions of data and possible associations with specific ABO blood groups and Rh status used descriptive means and ranges. Patient characteristics were compared by independent t-tests for continuous variables and the chi-squared (χ^2) test or Fisher's exact test for categorical variables. For the comparison of variables between groups, the Kruskal-Wallis test was used for asymmetrical distributions. P-values <0.05 were considered to be significant.

Results

Between 2004 and 2015 in Turkey, a total of 4,691 patients were diagnosed with breast cancer, of which 3,944 patients with histologically confirmed breast cancer had information on their blood group: type A, B, O, and Rhesus (Rh)-positive or Rh-negative.

The 3,944 patients with breast cancer were blood group, type A, B, O, and Rh-positive or Rh-negative, with a median age of 47.9 years (range, 18.2–89.6 years). Of the patients studied, 99.5% (3923/3,844) were women, and 0.5% (21/3944) were men. The distribution of ABO and Rh blood group of patients was similar to the general healthy Turkish population. Table 1 summarizes the characteristics of the patients according to ABO blood group.

Analysis of study patient data using the chi-squared (χ^2) test showed that patients with blood type O had a significantly smaller primary breast tumor size, or lower T stage (of the TNM staging classification) when compared with the other blood groups, which was confirmed using in multivariate analysis (P=0.007) (RR=0.69; 95% CI, 0.527–0.904).

The frequency of lobular breast cancer, overexpression of tumor cell estrogen receptor (ER), and the presence of metastasis were significantly increased in Rh-positive patients with breast cancer when compared with Rh-negative patients with breast cancer (Table 2). Multivariate analysis confirmed that distant metastases (P=0.007) (RR=1.63; 95% CI, 1.145–2.328) and the lobular histological type of breast cancer (P=0.047) (RR=2.21; 95% CI, 1.012–4.845) were significantly more frequent in Rh-positive patients with breast cancer when compared with Rh-negative patients with breast cancer.

Table 1. The characteristics of patients according to ABO blood group.

Blood groups		A	B	O	AB	p Value
Number of pts [n, (%)]		1721 (43.6)	586 (14.9)	1323 (33.5)	314 (8)	
Histology [n, (%)]	IDC	1085 (43.7)	398 (14.7)	916 (33.8)	215 (7.9)	0.936
	ILC	82 (42.9)	31 (16.2)	63 (33.0)	15 (7.9)	
	Mixt	219 (45.5)	75 (15.6)	149 (31.0)	38 (7.9)	
	DCIS	56 (37.1)	21 (13.9)	60 (39.7)	14 (9.3)	
	Others*	179 (44.0)	61 (15.0)	135 (33.2)	32 (7.9)	
ER status [n, (%)]	Positive	1280 (44.3)	436 (15.1)	951 (32.9)	223 (7.7)	0.262
	Negative	375 (41.1)	136 (14.9)	326 (35.7)	76 (8.3)	
	Missing	66 (46.8)	14 (9.9)	46 (32.6)	15 (10.6)	
PR status [n, (%)]	Positive	1172 (44.3)	394 (14.9)	866 (32.7)	214 (8.1)	0.349
	Negative	458 (41.3)	171 (15.4)	395 (35.6)	85 (7.7)	
	Missing	91 (48.1)	21 (11.1)	62 (32.8)	15 (7.9)	
HER2 status [n, (%)]	Positive	384 (45.9)	136 (16.3)	262 (31.3)	54 (6.5)	0.176
	Negative	1312 (43.1)	439 (14.4)	1038 (34.1)	257 (8.4)	
	Missing	25 (40.3)	11 (17.7)	23 (37.1)	3 (4.8)	
Tumor size (cm) [n, (%)]	≤2	564 (42.2)	192 (14.4)	488 (36.6)	91 (6.8)	0.020
	>2	1091 (44.2)	372 (15.1)	792 (32.1)	214 (8.7)	
	N/A	66 (47.1)	22 (15.7)	43 (30.7)	9 (6.4)	
Nodal involvement [n, (%)]	Negative	763 (43.7)	247 (14.1)	593 (33.9)	144 (8.2)	0.710
	Positive	872 (43.8)	308 (15.5)	654 (32.8)	158 (7.9)	
	N/A	86 (42)	31 (15.1)	76 (37.1)	12 (5.9)	
Metastasis	M0	1553 (43.6)	528 (14.8)	1193 (33.5)	287 (8.1)	0.967
	M1	150 (43.9)	53 (15.5)	114 (33.3)	25 (7.3)	
	Not available	18 (43.9)	5 (12.2)	16 (39)	2 (4.9)	

* Others includes tubular, mucinous, metaplastic and papillary carcinoma of breast.

Discussion

Because there was conflicting data in literature on the frequency of breast cancer individuals with different blood groups, the aim of this study was to investigate the association between A, B, O, Rhesus (Rh)-positive, and Rh-negative blood groups in a nationwide cohort of 3,944 patients diagnosed with breast cancer between 2004 and 2015 in Turkey. The findings of this study cohort showed that the distribution of ABO blood groups in patients with breast cancer was similar to that of the healthy Turkish population.

In a previously published small study, there were no significant difference in blood groups of human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients and controls [6]. Also, Gates et al. prospectively studied 3,107 patients with breast cancer and found that there was no association between ABO blood group and breast cancer risk [7]. Also, a Korean study did not show any difference in the distribution of blood groups of young patients with breast cancer when compared with an age-matched healthy population [8]. However, a study from Morocco showed that the incidence of breast cancer was increased in patients with blood group type B [9]. Published data from a meta-analysis showed that Caucasians with blood group type A were at an

Table 2. The characteristics of patients according to Rh group.

Blood groups		Rh positive		Rh negative		p Value
Number of pts [n, (%)]		3479	(88.2)	465	(11.8)	
Histology [n, (%)]	IDC	2402	(88.5)	312	(11.5)	0.008
	ILC	180	(94.2)	11	(5.8)	
	Mixt	422	(87.7)	59	(12.3)	
	DCIS	133	(88.1)	18	(11.9)	
	Others*	342	(84)	65	(16)	
ER status [n, (%)]	Positive	2571	(89)	319	(11)	0.042
	Negative	789	(86.4)	124	(13.6)	
	Missing	119	(84.4)	22	(15.6)	
PR status [n, (%)]	Positive	2346	(88.7)	300	(11.3)	0.440
	Negative	967	(87.2)	142	(12.8)	
	Missing	166	(87.8)	23	(12.2)	
HER2 status [n, (%)]	Positive	736	(88)	100	(12)	0.653
	Negative	2686	(88.2)	360	(11.8)	
	Missing	25	(40.3)	11	(17.7)	
Tumor size (cm) [n, (%)]	≤2	1180	(33.9)	155	(33.3)	0.843
	>2	2177	(62.6)	292	(62.8)	
	N/A	122	(3.5)	18	(3.9)	
Nodal involvement [n, (%)]	Negative	1749	(50.3)	243	(52.2)	0.723
	Positive	1549	(44.5)	198	(42.6)	
	N/A	181	(5.2)	24	(5.2)	
Metastasis	M0	3125	(89.8)	436	(93.8)	0.023
	M1	315	(9.1)	27	(5.8)	
	Not available	39	(1.1)	2	(0.4)	

* Others includes tubular, mucinous, metaplastic and papillary carcinoma of breast.

increased risk of developing breast cancer when compared with non-Caucasians [5]. These conflicting findings require clarification with large-scale, long-term, multi-center, controlled, and well-designed studies.

The present study was a large-scale, nationwide study. Analysis of patient data using the chi-squared (χ^2) test showed that patients with blood type O had a significantly smaller primary breast tumor size (or lower T stage) when compared with the other blood groups, which was confirmed using in multivariate analysis ($P=0.007$) (RR=0.69; 95% CI, 0.527–0.904). However, this finding is not supported by a previously published study by Klimant et al. who showed that breast cancer patients with

AB and O blood groups had larger tumor size when compared with patients with blood type A and B [10].

Although there have been previously published studies that showed no difference between tumor size and blood group, if the findings of the present study are correct, it would be expected that patients with blood type O would be more likely to have a more favorable prognosis, and studies on patient survival in breast cancer and blood type are needed. Of interest is a study that is supportive of the findings of the present study, which was recently published by Park et al. who showed from the prognostic results of a Korean nationwide study of young patients with breast cancer that women with breast

cancer who were <40 years-of-age, with blood group O had a more favorable prognosis [8]. However, tumor size is not the only prognostic factor for patients with breast cancer, and in the present study, no other significant associations were identified between ABO blood groups and factors that included patient age, breast tumor grade, stage, ER or HER2 status, nodal involvement, and distant metastasis. However, the findings of the present nationwide cohort study involving 3,944 women with breast cancer are consistent with those of the largest previously published study to date, published in 2012 by Gates et al. in a study that included 67,697 women, and that showed no association between ABO blood group and breast cancer risk or patient survival and no significant association between blood type and patient mortality due to breast cancer [7].

Worldwide, the Rh-negative trait is less common than the Rh-positive trait. Stamatakos et al. showed that relative risk of metastasis in patients with breast cancer who were Rh-negative was 4.2 times greater than for Rh-positive patients, but this was from a study that included a small number of patients [11]. However, the findings of the present large-scale nationwide cohort study showed that distant metastasis was 1.6 times more common in Rh-positive patients compared with Rh-negative patients with breast cancer. Also, Stamatakos et al. reported that histologically confirmed ductal breast cancer was more common in Rh-positive patient groups when compared with Rh-negative patient groups but their study also included a small number of patients with breast cancer [11]. However, the findings of the present study showed that lobular carcinoma (rather than ductal carcinoma) histology was more commonly seen in Rh-positive patients when compared with Rh-negative patients. Also, the findings of the present study showed that Rh-positive patients had more breast cancers with a luminal type of histology compared with Rh-negative patients. A type A luminal breast cancer is one that overexpresses ER and/or progesterone receptor (PR), and a type B luminal breast cancer overexpresses ER, PR, and HER2 and has a high cell proliferation rate.

This study had several limitations. A retrospective study was undertaken of a Turkish population, which relied on archived data from patient records and there was a lack of long-term patient follow-up. Detailed outcome data was unavailable, including local recurrence or metastasis, which would have been data required to evaluate associations between blood groups and patient prognosis from breast cancer. However, to

our knowledge, this was the largest cohort to have been studied in a Turkish population for the association between ABO and Rhesus blood groups and breast cancer.

Future studies are required to clarify the varied findings from the literature. Possible mechanisms for future study that might explain the association between cancer and blood group includes studies on Forssmann antigen which is structurally similar to the A antigen, and which has been studied in gastric and colonic mucosal changes, but has not been demonstrated in breast tissue [12]. Increased levels of some inflammatory mediators, including soluble intracellular adhesion molecule (ICAM)-1, E-selectin, and P-selectin might have a role in carcinogenesis or cancer progression in people with blood group A [13,14]. A further area for future study is the association between the expression of the ABH antigen in breast ductal or lobular carcinoma cells that might be involved with cancer-endothelial cell interactions and with metastasis and generation of an anti-tumor immune response [15]. Glycosylation is associated with ABO blood group antigens and the link between glycosylation and carcinogenesis is a potential future area of study [16].

Conclusions

The aim of this retrospective study was to investigate the association between A, B, O, Rhesus (Rh)-positive, and Rh-negative blood groups in a nationwide cohort of 3,944 patients diagnosed with breast cancer between 2004 and 2015 in Turkey. The main findings of this study showed that the type, grade, stage, and hormonal status of breast cancer showed no significant associations with ABO blood grouping. However, breast cancer patients with blood type O had a smaller tumor size, and patients with breast cancer who were Rh-positive had more luminal-type breast cancers that were estrogen receptor (ER)-positive tumors and with more metastases. Further studies are needed to understand the role of blood group antigens in carcinogenesis, cancer progression, and patient prognosis in breast cancer.

Conflict of interest

None.

References:

1. Aird I, Bentall HH, Roberts JAF: A relationship between cancer of stomach and the ABO blood groups. *Br Med J*, 1953; 1(4814): 799–801
2. Franchini M, Favalaro EJ, Targher G, Lippi G: ABO blood group, hypercoagulability, and cardiovascular and cancer risk. *Crit Rev Clin Lab Sci*, 2012; 49(4): 137–49
3. Edgren G, Hjalgrim H, Rostgaard K et al: Risk of gastric cancer and peptic ulcers in relation to ABO blood type: A cohort study. *Am J Epidemiol*, 2010; 172(11): 1280–85
4. Zhang BL, He N, Huang YB et al: ABO blood groups and risk of cancer: A systematic review and meta-analysis. *Asian Pac J Cancer Prev*, 2014; 15(11): 4643–50
5. Miao SY, Zhou W, Chen L et al: Influence of ABO blood group and Rhesus factor on breast cancer risk: A meta-analysis of 9,665 breast cancer patients and 244,768 controls. *Asia Pac J Clin Oncol*, 2014; 10(2): 101–8
6. Urun Y, Utkan G, Altundag K et al: ABO and Rh blood groups frequency in women with HER2-positive breast cancer. *J BUON*, 2012; 17(3): 457–60
7. Gates MA, Xu M, Chen WY et al: ABO blood group and breast cancer incidence and survival. *Int J Cancer*, 2012; 130(9): 2129–37
8. Park S, Kim KS, Kim JS et al: Prognostic value of ABO blood types in young patients with breast cancer; A nationwide study in Korean Breast Cancer Society. *Med Oncol*, 2017; 34(6): 118
9. Zouine S, Marnissi F, Otmani N et al: ABO blood groups in relation to breast carcinoma incidence and associated prognostic factors in Moroccan women. *Med Oncol*, 2016; 33(7): 67
10. Klimant E, Glurich I, Mukesh B, Onitilo AA: 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): 111–18
11. Stamatakis M, Kontzoglou K, Safioleas P et al: Breast cancer incidence in Greek women in relation to ABO blood groups and Rh factor. *Int Semin Surg Oncol*, 2009; 6: 14
12. Hakomori S, Wang SM, Young WW Jr.: Isoantigenic expression of Forssman glycolipid in human gastric and colonic mucosa: Its possible identity with “A-like antigen” in human cancer. *Proc Natl Acad Sci USA*, 1977; 74(7): 3023–27
13. Barbalic M, Dupuis J, Dehghan A et al: Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels. *Hum Mol Genet*, 2010; 19(9): 1863–72
14. Paterson AD, Lopes-Virella MF, Waggott D et al: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. 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(11): 1958–67
15. Lee AK, DeLellis RA, Rosen PP et al: ABH blood group isoantigen expression in breast carcinomas – an immunohistochemical evaluation using monoclonal antibodies. *Am J Clin Pathol*, 1985; 83(3): 308–19
16. Zouine S, Orfi Z, Kojok K et al: Immunohistochemical and genetic exploration of incompatible A blood group antigen expression in invasive micropapillary breast carcinoma: A case report. *Curr Res Transl Med*, 2017; 65(2): 71–76