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Influence of ABO blood group and rhesus factor on breast cancer risk: A retrospective analysis

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Abstract

Background and objective: Discussions surrounding the influence of ABO blood groups and Rh factor expressions on the development and progression of breast cancer has persisted over an extended period of time. This study sought to explore the connections between blood group/Rh and occurrence of breast cancer. Additionally, it aimed to elucidate the associations between blood group/Rh and some important prognostic characteristics in breast cancer, such as tumor grade and disease stage.

Methods: The study was retrospective observational analysis performed in Rizgary Teaching Hospital's Oncology Center in Erbil during the years 2021 and 2022 to investigate the associations between ABO blood group/Rh factor and the risk of breast cancer, including impacts on both the occurrence and the tumor characteristics.

Results: Upon analyzing 303 patients with breast cancer, the study disclosed a lack of statistically significant link between blood group/Rh and the occurrence of breast cancer when compared to the control group, as evidenced by a *p*-value of 0.608 for ABO blood group and 0.838 for Rh factor associations. Moreover, examination of a smaller subset of 187 patients revealed no statistically significant influence of blood group/Rh factor on either the tumor grade (P = 0.319 for ABO and P = 0.710 for Rh) or the disease stage of breast cancer (P = 0.925 for ABO and P = 0.876 for Rh).

Conclusion: These findings emphasize the importance of dispelling potential misconceptions, suggesting that blood groups may not be a decisive factor in predicting or understanding breast cancer. This may contribute to refining medical perspectives and guiding more targeted avenues for future research.

Keywords: ABO blood group; Rh factor; Breast cancer; Prognostic characteristics.

Introduction

In the present era, breast cancer poses a substantial global public health concern. In 2020, approximately 2.26 million people were diagnosed with breast cancer, making it the most prevalent cancer globally and the leading cause of cancer-related mortality among women.[1-4]

The development of breast cancer has been linked to various genetic and environmental factors, including age, onset of menstruation/menopause, family history of breast cancer, obesity, and lifestyle habits such as diet and smoking.[5]

Furthermore, there has been ongoing discussion regarding the role of blood group and Rhesus factor expressions as potential risk factors in the development and progression of breast cancer.[6-8] "ABO" blood types are polymorphic antigenic substances located on the surface of red blood cells (RBCs) and various other cells within the body. Karl Landsteiner discovered the "ABO" blood group in 1900, while the Rhesus (Rh) factor was identified in 1940 by Landsteiner and Wiener. These ABO and Rhesus factors constitute the principal human blood type systems, playing a crucial role in transfusion medicine and

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the pathology of numerous diseases.[9,10]
Beyond red blood cells, blood group antigens are present on leukocytes, specific tissues, plasma proteins, platelets, and various cell surface enzymes. Additionally, these antigens can be found in bodily fluids like saliva, sweat, breast milk, seminal fluid, urine, gastrointestinal secretions, and amniotic fluid in a soluble form.[11]
From a pathophysiological perspective, the ABO blood type antigens manifest different phenotypes and genetically determined glycoconjugate structures situated on the surface of red blood cells, actively influencing cellular physiology and pathology. Nevertheless, the absence of antigens in certain blood groups has led to debates regarding the connection between the ABO blood group and susceptibility to specific infectious and noninfectious diseases. In other words, the presence or absence of antigens in various blood types contributes to alterations in both the morphology and function of red blood cell membranes. The functions linked to blood type structures can establish associations between blood groups in both diseases and overall health.[12,13]
The glycoconjugate structures present on red blood cells serve various functions, such as acting as receptors for external ligands, viruses, bacteria, and parasites. They also function as transporters, channels, adhesion molecules, structural proteins, and enzymes. While the precise mechanisms linking blood group antigens to diseases through adhesion molecules are not fully understood, a significant number of these structures contribute to normal red blood cell development; some of them function as cell adhesion molecules (CAMs) that play roles in a number of human diseases.[14]
During the 1960s and 1970s, extensive global epidemiological studies were conducted, widely proposing associations between the human ABO blood group and susceptibility to several diseases.[15,16] Both ABO and Rhesus blood types were found to be correlated with various infectious and non-infectious diseases, including cancers like gastric and colorectal malignancies.[17,18]
Concerning breast cancer, while several previous studies commonly indicated no connection,[19,20] more recent investigations have hinted at a potential link between blood type and the occurrence of breast cancer.[21-23] Furthermore, certain studies propose a potential correlation between different expressions of blood group antigens and certain prognostic factors, such as the pathological stage of the disease, in women diagnosed with breast cancer.[24,25]
Due to long-term conflicting evidence regarding the correlation between blood type and breast cancer in various parts of the world, this study was carried out to determine whether there is a connection between ABO blood groups/Rh factor types and the occurrence of breast cancer in our region. Additionally, the study sought to examine whether blood group/Rh has any effect on crucial prognostic tumor characteristics such as the tumor's histological grade and disease stage at the time of breast cancer diagnosis.

Methods

Study Design and Data Collection:

The study was conducted in a two-part retrospective observational analysis to investigate the associations between ABO blood group/Rh factor and the risk of breast cancer, including impacts on both the occurrence and the tumor’s prognostic characteristics such as tumor grade and disease stage.
In the first part, a larger dataset was utilized, comprising analysis of the medical records of 303 breast cancer patients who sought management in the Oncology Center at Rizgary Teaching Hospital in Erbil over a two-year period (2021 and 2022) to explore the relationship between cases (cancer patients) and controls. The diagnosis of breast cancer of each patient was confirmed depending on the

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histopathological reports of surgical tissue specimens obtained from biopsy and/or mastectomy, a copy of which was preserved in the patients' hospital records. Also, the case-notes of each patient included a copy of their ABO blood group and Rhesus factor type, which was investigated serologically upon registration of the patients in the hospital. For the control group, a substantially larger dataset about blood group and Rh factor was obtained from the records of 55,756 individuals who visited Erbil's Central Blood Bank over the course of a year for the purpose of blood donation.

Subsequently, the second part of the study focused on examining the potential correlations between blood groups and some prognostically important breast cancer characteristics, specifically tumor grade and disease stage. For this aspect, a smaller subset of 187 cancer patients at Rizgary Oncology Center from the year 2021 was analyzed. Tumor grades were determined through histopathology and immunohistochemistry reports in the patients' case-notes. Three grades were identified: grade I, grade II and grade III, which represented low, medium and high cancer histological grades respectively, based on the degree of cellular differentiation. In addition to the histopathology documents, medical imaging reports such as CT scans and MRI scans were employed for the purpose of tumor staging based on the TNM Staging System of Union for International Cancer Control (UICC), 8th edition.[26]

This divides breast cancer into five stages from stage Zero to stage IV. Stage Zero represents carcinoma *in situ*, stages I and II represent early invasive breast cancer and stages III and IV represent locally advanced and metastatic cancer respectively. This comprehensive approach, integrating histopathological assessments and imaging data, aimed to present a thorough and precise portrayal of the breast cancer cases in this study.

Statistical Analysis: Differences in ABO blood group and Rh factor frequencies among both cancer patients and control samples, as well as the association of ABO/Rh blood type with breast cancer incidence, were assessed using Pearson Chi-square test. The Statistical Package for Social Sciences (SPSS v.25) software was utilized to calculate the associations between blood groups and prognostic characteristic factors in breast cancer using both Pearson Chi-Square and Fisher's Exact tests, with the latter specifically applied for datasets with small frequencies. Statistical significance required a two-sided *P*-value of less than 0.05.

Ethical Consideration: The study was approved by the Research Ethics Committee in Hawler Medical University/ College of Dentistry in May 2023. There were minimal ethical implications since the study was retrospective; and the participants' identities were protected by assigning each single patient with a specific serial number.

Results

The retrospective analysis involved the medical records of 303 women diagnosed with breast cancer. Table (1) displays the overall distribution of ABO blood groups and Rh factors among both breast cancer patients and controls. An examination of the table breakdown reveals a nearly identical prevalence of blood groups and Rh factors between the two studied groups. For instance, approximately 37% of the records in both groups were blood group "O," just under one-third were blood group "A", around a quarter of them were blood group "B", and a much smaller number in each group were reported to have blood group "AB". Similarly, roughly 90% of individuals in either studied groups were Rh positive, with the remaining being Rh negative. Generally, despite minor numerical variations, there were no statistically significant differences observed in regard to the blood group and Rh status between cancer patients and

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the control group. Additionally, the study involved the association of each single blood group, compared to others, with the occurrence of breast cancer. As evident from Table (2), there was no statistically significant association between individual blood types and the occurrence of breast cancer.

Table 1 Distribution of ABO Blood Groups and Rh Factor between Breast Cancer Patients and Control Group

	Cancer Patients (n=303) No. (%)	**Control Group (n=55756) No. (%)**	***P*-value (Chi-Square)**
Blood Group			
O	113 (37.3)	20724 (37.2)	0.608
A	93 (30.7)	17363 (31.1)	
B	79 (26.1)	13359 (24.0)	
AB	18 (5.9)	4310 (7.7)	
Rh Factor			
Rh+	271 (89.4)	49662 (89.1)	0.838
Rh-	32 (10.6)	6094 (10.9)	
Total	303 (100)	55756 (100)	

Table 2 Comparison of Individual Blood Groups versus Others in Breast Cancer Patients and Control Group

Blood Group	**Breast Cancer (n=303) No. (%)**	**Control Group (n=55756) No. (%)**	**Odds Ratio**	**95% Confidence Interval**	***P*-value**
"O"	113 (37.3)	20724 (37.2)	1.01	(0.80 – 1.27)	0.964
Others (A, B, AB)	190 (62.7)	35032 (62.8)			
"A"	93 (30.7)	17363 (31.1)	0.98	(0.77 – 1.25)	
Others (O, B, AB)	210 (69.3)	38393 (68.9)			0.867
"B"	79 (26.1)	13359 (24.0)	1.12	(0.87 – 1.45)	0.390
Others (O, A, AB)	224 (73.)	42397 (76.0)			
"AB"	18 (5.9)	4310 (7.7)	0.75	(0.47 – 1.22)	0.245
Others (O, A, B)	285 (94.1)	51446 (92.3)			

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Regarding the distribution of tumor grade as a prognostic factor in breast cancer, as it is seen in Table 3, which reveals the analysis of the 187 patient records who had detailed information on their tumor characteristics, only 7.0% of the patients had low-grade (grade I) disease, more than half of them presented with intermediate-grade (grade II) disease, and 39% of the patients had high-grade (grade III) disease.

Table 3 also shows the associations between blood groups/Rh factor and breast cancer tumor grade. It demonstrated that, despite some numerical differences, both ABO blood type (*P*-value 0.319) and the Rh factor (*P*-value 0.710) did not exert any statistically significant influence on the tumor grade at the time of breast cancer diagnosis.

Table 3 Relations between ABO Blood Group/Rh Factor and Tumor Grade. (n=187)

		Tumor Grade				***P*-value (Exact Sig.)**
		I	**II**	**III**	**Total**	
		No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	
ABO Blood Group	O	3 (4.5)	36 (54.0)	28 (41.5)	67 (35.8)	0.319
	A	8 (12.7)	31 (49.2)	24 (38.1)	63 (33.7)	
	B	2 (4.3)	30 (63.8)	15 (31.9)	47 (25.1)	
	AB	0 (0.0)	4 (40.0)	6 (60.0)	10 (5.4)	
Rhesus Factor	Rh+	11 (6.6)	89 (53.6)	66 (39.8)	166 (35.8)	0.710
	Rh-	2 (9.5)	12 (57.2)	7 (33.3)	21 (33.7)	
Total		13 (7.0)	101 (54.0)	73 (39.0)	187 (100)	

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Finally, regarding the 'disease stage' in the 187 studied breast cancer patients, Table 4 reveals that the majority of the patients (at around 60%) had early-stage (stages 0, I and II) disease; a quarter of them had locally advanced (stage III) disease; and only about 13% of the patients had distant metastatic disease at the time of initial breast cancer presentation. Concerning the question of whether blood group and Rh factor have effects on the above-described disease stages, Table 4 demonstrates that there was no any statistically meaningful association between neither blood group (*P*-value 0.925) nor the Rh factor (*P*-value 0.876) and the disease stage at the time of breast cancer diagnosis.

Table 4 Relations between ABO blood group/rhesus factor and disease stage. (n=187)

		Breast Cancer Disease Stage						***P*-value (Exact Sig.)**
		Zero (*In situ*) No. (%)	**I No. (%)**	**II No. (%)**	**III No. (%)**	**IV No. (%)**	**Total No. (%)**	
ABO Blood Group	O	1 (1.5)	8 (11.9)	31 (46.3)	16 (23.9)	11 (16.4)	67 (35.9)	0.925
	A	2 (3.2)	9 (14.3)	26 (41.2)	18 (28.6)	8 (12.7)	63 (33.7)	
	B	1 (2.1)	6 (12.8)	22 (46.8)	14 (29.8)	4 (8.5)	47 (25.1)	
	AB	0 (0.0)	3 (30.0)	5 (50.0)	1 (10.0)	1 (10.0)	10 (5.4)	
Rhesus Factor	Rh+	4 (2.4)	22 (13.2)	76 (45.8)	43 (25.9)	21 (12.7)	166 (88.8)	0.876
	Rh-	0 (0.0)	4 (19.0)	8 (38.1)	6 (28.6)	3 (14.3)	21 (11.2)	
Total		4 (2.1)	26 (13.9)	84 (44.9)	49 (26.3)	24 (12.8)	187 (100)	

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Discussion

The first reports suggesting a link between blood group and an elevated cancer risk emerged in the fifties of last century.[27,28] Since then, numerous studies have explored the involvement of ABO blood types in various human disorders, including cardiovascular diseases and cancer.[29-31]

While the precise mechanisms connecting the ABO/Rh blood system to cancer remain uncertain, potential explanations include altered expression of blood group antigens on cancer cell surfaces, impacting cell motility, apoptosis sensitivity, and immune evasion—an influential factor in malignant progression.[32]

Additionally, this association might influence the regulation of circulating pro-inflammatory molecules (e.g., tumor necrosis factor-alpha) and adhesion molecules (e.g., soluble E-select in, *P*-select in, and intercellular adhesion molecule-1), suggesting the involvement of these antigens in the systemic inflammatory response—a potential cancer risk mechanism.[33]

Despite these proposed explanations, our study revealed that the distribution of ABO blood types in studied breast cancer patients mirrored that of the general population, with no correlations found between clinical and prognostic characteristics (such as breast cancer stage and histopathological tumor grade) and ABO/Rh blood type. Similar findings were reported in some previous studies, including one in Egypt in 2014 and a national cohort in Turkey in 2018, both found no correlation between breast cancer risk characteristics and blood type.[21-34] A study in Iran showed that blood type is not a risk factor for breast cancer development when comparing Isfahan women with breast cancer to the healthy population.[8] Similarly, a new Iraqi study in 2023 concluded that there was no correlation between ABO blood types and breast cancer.[35]

However, conflicting results exist, with some studies supporting significant associations between blood type and breast cancer risk. For instance, a study from Saudi Arabia, revealed that blood group "A" and "Rhesus positive" have higher risk of breast cancer occurrence.[36] Another study from Denmark concluded that, compared to blood group "O", other blood groups were associated either with higher or lower risk of cancer occurrence at different anatomical sites.[37] Also a study from Morocco showed that blood type A and AB were associated with high incidence of lymph node positive breast cancer.[25]

In general, discrepancies in the study results done worldwide in regard to associations between various blood groups and risk of diseases may have stemmed from variations in population characteristics, limited study sizes, and differences in ABO distribution across different parts of the world.[38] Concerning the present study, a sample size of 303 patients offers valuable insights; however, being retrospective and reliant on hospital records introduce certain limitations. The data's completeness and accuracy are contingent upon the records available, potentially leading to information gaps. Additionally, inherent to retrospective designs, selection bias may affect the representativeness of the findings. Controlling for all potential confounding variables is challenging, and the generalizability of the results beyond the studied population may be limited.

Conclusion

In conclusion, this study aimed at exploring possible associations between blood groups and breast cancer risk, as well as tumor prognostic characteristics. The findings revealed no significant correlation between blood groups and prevalence of breast cancer. Moreover, there was no apparent link between blood groups and key tumor characteristics, including grade and disease stage.

From a clinical perspective, these results underscore the need to debunk potential

misconceptions, indicating that blood groups may not be a decisive factor in predicting or understanding breast cancer characteristics. This clarity contributes to refining medical perceptions and guiding more targeted paths for future research, which could benefit from prospective designs and a more comprehensive exploration of genetic and environmental factors influencing breast cancer.

Competing interests

The author declares that he has no competing interests.

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