

The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

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Abstract

Background: Breast cancer is the most common cancer among women and one of the most important causes of death among them. Many of previous studies showed a strong association between ABO, Rh blood groups, and the occurrence of malignant tumors.

Objectives: The present study aimed to determine the association between ABO blood groups and Rhesus factor with prevalence of the breast cancer.

Methods: In this study, we identified 50 research documents from data based search engines. The research papers were selected by using the primary key-terms including breast cancer, ABO blood type, and Rhesus blood type. We reviewed the 36 papers that harmonized our criteria were comprised and remaining papers were excluded. The current study was included more than 847811 normal subjects as control and more than 19208 breast cancer patients for ABO blood groups and more than 251939 subjects as control and more than 11116 breast cancer patients for Rh factor.

Results: Blood group (A) has high incidence of breast cancer (40.62%), blood group (O) has (33.46%); (B) (17.31%) and blood group (AB) has (8.091%) incidence of breast cancer. Blood group (A) has the highest and blood group (AB) has least association with breast cancer. Rhesus positive (Rh⁺) blood group has high incidence of breast cancer (87.20%) and Rhesus negative (Rh⁻) blood group has least association with breast cancer (12.80%).

Conclusion: It can be concluded that blood group (A) and Rh⁺ have a high risk of breast cancer, while blood type (AB) and Rh⁻ are at low risk of breast cancer. So, physicians should carefully monitor the females with blood group (A) and Rh⁺ as these females are more prone to develop breast cancer. To reduce the prevalence of the breast cancer and its burden, screening, and preventive programs for breast cancer especially in young women are highly recommended. Further studies are necessary to determine the mechanisms by which ABO blood type may influence the risk of breast cancer.

Keywords: ABO blood group system, Rhesus factor, Rh, Blood type, Breast cancer.

INTRODUCTION

Worldwide more than 20 million people are living with cancer and its number is expected to be more than 30 million by 2020 [1-3]. Breast cancer is the most common cancer among women and one of the most important causes of death among them [4]. It is a life threatening disease among young premenopausal women affecting their sexuality, femininity, body image, and maternal issues following mastectomy may lead the women to face psychiatric co-morbidity

[3]. It is the second leading cause of cancer deaths in women [5-8], affecting more than 2 million females each year. In 2018, breast cancer took the lives of 627,000 women, accounting for 15% of all cancer deaths among females [8, 9]. The incidence of breast cancer has been allied with numerous factors including ageing, obesity, delayed childbearing, menopause, genetics, environment, diet [8, 9], and lifestyle are the most important ones, and also many factors such as parities, lactation, and exercise play important roles in reducing the risk of this disease [4].

The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

ABO blood types are polymorphic, antigenic, genetic substances which are established on the Red Blood Cells (RBCs) surface and some other cells and tissues. In 1900, Karl Landsteiner discovered the ABO blood group. ABO and Rhesus blood types are the major human blood type system with principal importance in transfusion medicine [10, 11]. The ability of type of ABO groups to induce special cancer reliable on population racism and genetic susceptible [5].

Many of previous studies showed a strong association between ABO, Rh blood groups, and hemostasis, thrombosis, cardiovascular, metabolic, and various malignant diseases, such as salivary gland tumors, ovarian tumors, upper urinary tract tumors, pancreatic cancer, duodenal ulcer, colorectal cancer, gastric cancer, small cell carcinoma of lung, breast cancer, thyroid disorders, coronary heart disease, and hypercholesterolemia [3, 12-26].

The association of breast cancer and the blood type has had different degrees in various studies. Previous studies reported that ABO blood groups may be useful as a predisposing or prognostic factor in breast cancer [8, 27-32]. The study of Prakash *et al.*, [3] showed that the risk of developing breast cancer was found to be insignificant with ABO blood type ($p=0.97$). Although the largest percentage of the global population has the blood group O+, Meo, [8] and Meo *et al.*, [11] found that blood group A⁺ has a high risk while blood type AB⁻ has a low risk of breast cancer. The studies of Meo *et al.*, [11], Guleria *et al.* [33], Akhtar *et al.* [34], Sahar *et al.*, [35], and Aly *et al.*, [36] showed that a strong correlation between the ABO group type and breast cancer and the highest frequency and percentage of patients with breast cancer was observed in blood group type A. Miao *et al.*, [37] reported that Caucasians with blood type A may have a higher risk of breast cancer than other Caucasians. No association was found in any other blood type or any other population. Also, recent meta-analysis data has indicated that blood group A conferred an increased risk for developing breast cancer [26, 37, 38]. Many previous studies referred to A blood group was higher incidence to breast cancer and followed by O type than other groups [5, 15, 39, 40]. Zouine *et al.*, [41] were noticed that the incidence of breast cancer among Moroccan women was increased among very young women with blood group A and among the blood group B patients aged over 70 years. Bhartiya *et al.*, [32] reported that the blood group A and AB are more

prone to breast cancer than other blood groups (B and O) as they are more common in control population, Other studies observed positive associations with type A or B among women with a family history of breast cancer [15]. On the other hand, the study performed by Holdsworth *et al.*, [42] reported B or AB blood groups to be a prognostic factor for breast cancer. The study of Guleria *et al.*, [33] reported that the B blood group was more susceptible to affect breast cancer in Indian patients. Also, Iodice *et al.*, [43] reported the incidence was higher among patients with O blood group and was statistically insignificant ($p=0.60$). Kumar *et al.*, [44] reported that blood group O has more chances to develop breast cancer, while blood group B also has increased incidence of breast cancer. More than two third patients of breast cancer belong from these two groups. While blood group AB and A has less incidence of breast cancer comparatively. It is quite clear from study that blood group O people were more prone to develop breast cancer. The risk of breast cancer in both familial and sporadic cases are related to the ABO blood group and the bilateral familial breast cancer has more prevalence in B-blood group than sporadic cases [3, 30, 45]. Cihan *et al.*, [46] noted the overall and disease-free survival was highest in O blood group followed by A blood group in breast cancer. This difference in association in blood groups and breast cancer incidence may be attributed to the difference in geographical location as well as the ethnic population [5, 47].

ABO blood group genes are mapped at 9q34.2 region in which genetic alteration is common in many cancers. Thus, blood group antigen expression may be affected by genetic change of tumor [3, 48]. So, alterations in ABO antigen expression on the surface of malignant cells have been observed for a variety of tumor types, including breast cancer [49].

Antigen A is associated with high risk of developing aggressive ductal cancer in 166 women [50]. Klimant *et al.* [51] recorded that breast cancer patients with AB and O blood groups had larger tumor size when compared with patients with blood type A and B. On the other hand, Akin and Altundag, [26] reported that breast cancer patients with blood type O had a significantly smaller tumor size compared with patients with blood types A or B. In Iran, Amini *et al.*, [52] found that there is a significant relationship between the blood type and the size of tumor ($P=0.035$), axillary lymph nodes involvement ($P=0.001$), and the

The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

prognosis of the breast cancer (P=0.014). A blood group is more frequent in patients with breast cancer in comparison with O-blood group. Also, the presence of B-antigen shows association with poor prognosis of breast cancer.

Shiryazdi *et al.*, [7] and Meo *et al.*, [11] reported that frequency distribution numbers of women developed breast cancer with Rh- were less than numbers patients with Rh+. Also, Prakash *et al.*, [3] reported that most of the respondents had Rh positive with breast cancer and was also found to be insignificant. Similarly, Miao *et al.*, [37] reported that the Rh factor had no association with the risk of breast cancer

RESEARCH METHODOLOGY

Methods

In this study, we identified 50 research documents from data based search engines. The research papers were selected by using the primary key-terms including

breast cancer, ABO blood type, and Rhesus blood type. The current study was included more than 847811 normal subjects as control and more than 19208 breast cancer patients for ABO blood groups and more than 251939 subjects as control and more than 11116 breast cancer patients for Rh factor. All articles in which breast cancer, ABO, and Rhesus factor blood groups were reported and considered appropriate for inclusion without limitations on research documents of the publications. We reviewed the 36 papers that harmonized our criteria were comprised and remaining papers were excluded. Table. 1&2 shows The percentages of ABO blood groups and Rhesus factor in normal subjects and breast cancer patients in the studied literatures.

Statistical Analysis

The data were computed into the computer; percentages were calculated and analyzed by using the GraphPad Prism for Windows, version 5.0.

Table1. Association between blood groups and breast cancer

No.	Country	Controls				Breast cancer Patients				References		
		Number of Normal Subjects	A (%)	B (%)	AB (%)	O (%)	Number of Patients	A (%)	B (%)		AB (%)	O (%)
1.	UK	37026	40.4	9.1	3.0	47.6	1008	41.4	10.1	2.9	45.6	Aird <i>et al.</i> , [53]
2.	USA	79699	38.4	11.1	4.1	46.4	1000	41.3	11.1	2.9	44.7	Goldenberg <i>et al.</i> , [54]
3.	India	2273	26.1	34.2	7.1	32.6	84	21.4	35.7	8.3	34.5	Mitra <i>et al.</i> , [55]
4.	Norway	31491	48.1	8.6	3.7	39.6	1600	51.9	6.8	3.5	37.8	Hartmann <i>et al.</i> , [56]
5.	USA	550	29.8	17.1	5.1	48.0	444	28.2	16.9	6.5	48.4	Newell <i>et al.</i> , [57]
6.	Tunis	-	-	-	-	-	581	35.7	19	16.6	28.5	Mourali <i>et al.</i> , [27]
7.	USA	19100	39.3	10.7	3.5	46.5	2548	41.6	10.0	3.7	44.6	Anderson and Haas, [15]
8.	UK	29797	41.2	8.4	3.2	47.3	1001	40.3	8.2	3.1	48.5	Holdsworth <i>et al.</i> , [42]
9.	Iceland	16678	31.9	10.6	2.4	55.1	532	32.5	12.8	0.9	53.8	Tryggvadottir <i>et al.</i> , [39]
10.	China	24511	27.7	25.8	6.6	39.9	286	30.8	27.3	6.3	35.7	Wang <i>et al.</i> , [58]
11.	China	3277	30.1	32.2	10.4	27.3	210	24.3	28.1	13.8	33.8	Zou <i>et al.</i> , [59]
12.	Iraq.	279	26	28	8	38	200	60	20	10	10	Mehdi <i>et al.</i> , [5]
13.	Yemen	137	28.47	18.24	13.14	40.15	137	34.3	-	-	30.65	Al-Kahiry <i>et al.</i> , [60]
14.	Uruguay	549	30.2	6.2	7.7	55.9	252	61.2	3.3	11.2	24.3	Ronco <i>et al.</i> , [61]
15.	Turkey	1864	41.7	17.2	7.1	33.9	565	43.2	15.6	8.5	32.7	Dede <i>et al.</i> , [62]
16.	Greece	300	43.3	9.7	5.7	41.3	166	47.6	13.9	5.4	33.1	Stamatikos <i>et al.</i> , [30]
17.	India.	2640	18.6	40.5	11.4	29.5	462	42.4	30.3	6.1	21.2	Akhtar <i>et al.</i> , [34].
18.	China	1448	34.6	24.7	9.4	31.3	76	44.7	15.8	10.5	28.9	Li, [63]
19.	Iran.	-	-	-	-	-	134	16.4	30.6	28.4	24.6	Amini <i>et al.</i> , [52]
20.	Turkey.	204,553	41	16	8	35	1740	44	16	8	32	Urun <i>et al.</i> , [31]
21.	USA	1090	35.6	13.5	7.9	43	3107	36.56	14	8.11	41.33	Gates <i>et al.</i> , [64]
22.	Iraq	300	29.4	20.6	14	36	250	64.0	9.6	8.4	18.0	Sahar <i>et al.</i> , [35]
23.	Egypt.	92	39.1	18.4	9.7	32.6	160	53.1	17.5	7.5	21.8	Aly <i>et al.</i> , [36]
24.	Turkey	-	-	-	-	-	335	63	14.3	5.1	17.6	Cihan [46]
25.	Iran.	376	31.64	22.79	4.88	40.69	173	28.9	23.7	5.2	42.2	Flavarjani <i>et al.</i> , [65]
26.	Egypt.	1200	33.08	24	9.17	33.75	111	39.64	17.12	12.61	30.63	Mansour <i>et al.</i> , [66]
27.	India.	220	13.64	39.09	7.27	40	164	32.32	25	15.24	27.44	Bhartiya <i>et al.</i> , [32]
28.	India.	200	28	37.5	12.5	22	400	21.2	35.1	7.3	36.4	Kumar <i>et al.</i> , [44]
29.	Iran	43126	26	31	9	34	197	65.5	9.1	4	21.4	Shiryazdi <i>et al.</i> , [25]
30.	Iran	81	28.4	23.5	8.6	39.5	76	43.42	15.78	9.21	31.57	Payandeh <i>et al.</i> , [67]
31.	India	-	-	-	-	-	206	36.89	32.52	7.28	23.3	Saxena <i>et al.</i> , [68]
32.	USA	-	-	-	-	-	283	38	14	5	43	Yu <i>et al.</i> , [69]
33.	India	-	-	-	-	-	278	27.70	17.27	19.78	35.25	Prakash <i>et al.</i> , [3]
34.	Morocco.	344954	33.89	15.08	4.33	46.05	442	29.64	19.91	3.62	46.83	Zouine <i>et al.</i> , [41]
35.	Saudi Arabia	-	-	-	-	-	-	45.88	16.16	6.27	31.69	Meo <i>et al.</i> , [11]
36.	Turkey	-	-	-	-	-	-	43.6	14.9	8	33.5	Akin and Altundag, [26]

The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

Table2. Association between Rhesus factor and breast cancer

No.	Country	Number of Normal Subjects	Controls		Number of Patients	Patients		References
			Rh+ (%)	Rh- (%)		Rh+ (%)	Rh- (%)	
1.	Uruguay	549	70.24	29.76	252	76.14	23.86	Ronco <i>et al.</i> , [61]
2.	Turkey	1864	87.88	12.12	565	87.08	12.92	Dede <i>et al.</i> , [62]
3.	Greece	300	89	11	166	93.37	6.63	Stamatakos <i>et al.</i> , [30]
4.	Boston, USA	1090	77.75	22.25	3107	78.69	21.31	Gates <i>et al.</i> [64]
5.	Turkey.	204,553	87	13	1740	88	12	Urun <i>et al.</i> , [31]
6.	USA	-	-	-	283	89	11	Yu <i>et al.</i> [69]
7.	Turkey	-	-	-	335	82	18	Cihan, [46]
8.	Iran	376	89.08	10.92	173	97.1	2.9	Flavarjani <i>et al.</i> [65]
9.	Iran	81	91.4	8.6	76	93.42	6.58	Payandeh <i>et al.</i> [67]
10.	Iran	43126	85	15	197	93.4	6.6	Shiryazdi <i>et al.</i> [25]
11.	India	-	-	-	278	78.06	21.94	Prakash <i>et al.</i> , [3]
12.	Saudi Arabia	-	-	-	-	88.31	11.69	Meo <i>et al.</i> , [11]
13.	Turkey	-	-	-	3944	88.2	11.8	Akin and Altundag, [26]

RESULTS

Data in table 3 and figures (1-4) demonstrate the association of ABO blood groups and the risk of breast cancer. Blood group (A) has high incidence of breast cancer (40.62% VS. 32.96%, P=0.0058), blood group (O) has (33.46% t); (B) (17.31%) and blood group (AB) has (8.091%) incidence of breast cancer. Blood

group (A) has the highest and blood group (AB) has least association with breast cancer.

Also, table 3 and figures (5 & 6) show a relationship of Rh+ and Rh- blood groups and breast cancer. Rhesus positive (Rh+) blood group has high incidence of breast cancer (87.20%) and Rhesus negative (Rh-) blood group has least association with breast cancer (12.80%).

Table3. Mean percentages and stander deviations of blood groups in normal subjects and breast cancer patients

Groups Blood Groups	Normal subjects	Breast Cancer patients	P value
	Mean±SD	Mean±SD	
A	32.96±7.607	40.62±12.30	0.0058
B	20.14±10.16	17.31±8.194	0.3337
AB	7.364±3.164	8.091±5.375	0.9261
O	39.52±7.999	33.46±9.772	0.0139
Rh+	83.31±6.658	87.20±6.339	0.0764
Rh-	16.69±6.658	12.80±6.339	0.0764

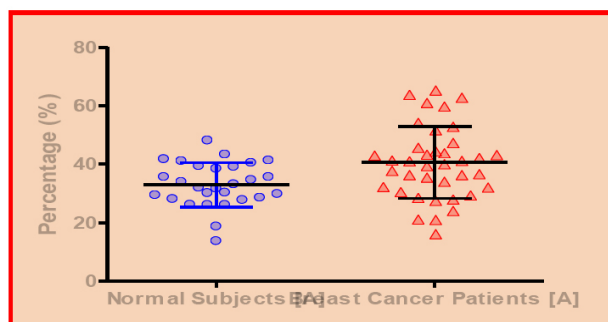


Figure1. Distribution, mean, and standard deviation of percentages of (A) blood group in normal subjects and breast cancer patients.

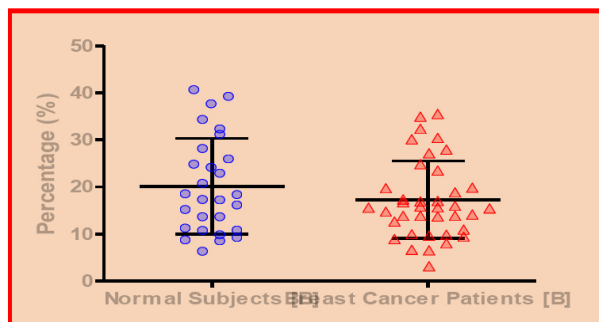


Figure2. Distribution, mean, and standard deviation of percentages of (B) blood group in normal subjects and breast cancer patients.

The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

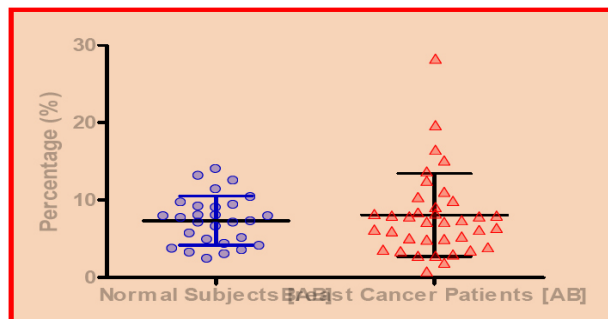


Figure3. Distribution, mean, and standard deviation of percentages of (AB) blood group in normal subjects and breast cancer patients.

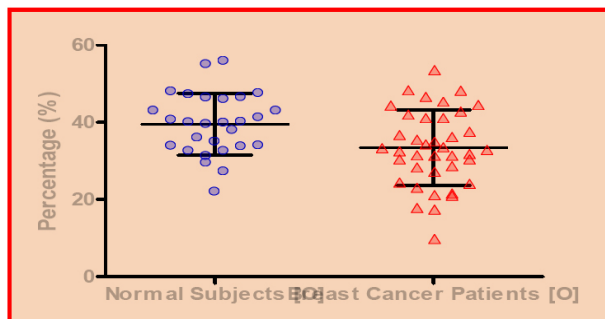


Figure4. Distribution, mean, and standard deviation of percentages of (O) blood group in normal subjects and breast cancer patients.

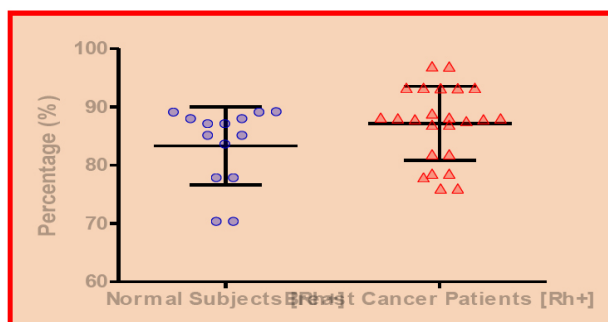


Figure5. Distribution, mean, and standard deviation of percentages of (Rh+) blood group in normal subjects and breast cancer patients.

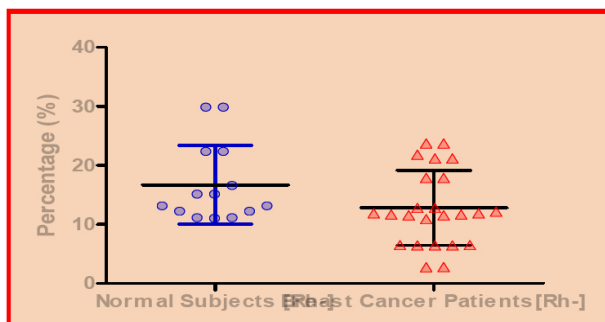


Figure6. Distribution, mean, and standard deviation of percentages of (Rh-) blood group in normal subjects and breast cancer patients.

DISCUSSION

Human malignancies such as colon, breast and prostate cancer as the blood group carbohydrates expressed on cell surface of metastasis cancer cells function as cell adhesion molecules. The loss or presence of blood group antigens can increase cellular motility or facilitate the interaction between tumor cells and endothelial cells [40, 44]. Blood group A may influence the systemic inflammatory response as they found associations between the genotype of the A blood group antigen and circulating levels of soluble intercellular adhesion molecule 1, E-selection and P Selection suggesting that increased incidence of breast cancer in blood group A cases [3, 26, 41, 70-73]. Tumor necrosis factor- α (TNF- α) is a key mediator of apoptosis. At low serum levels, it acts as an angiogenic factor and facilitates the development of cancer [41, 74]. This marker of inflammation is found in low levels in serum of blood group A or B patients [41, 75]. The expression of blood group A has been reported to increase resistance to apoptosis and prevent leukocyte recognition of the tumor cell, thus enabling the latter to escape the immune system control [41,

73, 76]. The plasma concentration of this molecule was associated with multiple SNPs variations within the ICAM gene and SNPs in the ABO locus [41, 71, 77]. The Von Willebrand factor (VWF), plasma glycoprotein that acts as an adhesive molecule, bonds between platelets and endothelial cells and plays a critical role in angiogenesis [41, 78, 79]. Indeed, it was detected at high levels in the serum of blood type non-O patients suffering from cancer [41, 80]. Also, blood group A individuals have a very low immunologic response to T and Tn antigens because they share the same sugar (N-acetylgalactosamine). This allows the cancer cells to bypass the immune system and replicate with little interference from the type A antibodies [3, 81]. In addition, modified expression of blood group antigens on the surface of cancer cells may also alter cell motility with important implications for malignant progression [82]. It has been speculated that a degree of the susceptibility to breast cancer, from a gene perspective, might be a result of a breast cancer susceptibility locus linked to the ABO locus located on band q34 of chromosome 9 [29, 44]. Deletion or reduction of histo-blood group A or B antigen in tumor of A or B individual of correlated with the degree of

malignancy and metastatic potential in many types of human cancers. The expression of histo-blood group A antigen has been reported to increase resistance to apoptosis and facilitate escape from immune control in rat colon carcinoma cells [5, 33, 73].

The increased risk of development of gastric and colonic cancers in patients with blood group A has been explained by the expression of Forssmann antigen in these cancers. Forssmann antigen is structurally similar to the blood group antigen A. Because of this similarity, antibodies to A may also attack precancerous and cancerous cells expressing this antigen. People with blood groups A and AB lack antibodies to A and hence are more prone to develop these carcinomas [83]. This might also apply to the mechanism behind the higher prevalence of blood group A and AB in breast cancer patients [29].

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 [26, 84].

CONCLUSION

It can be concluded that blood group (A) and Rh+ have a high risk of breast cancer, while blood type (AB) and Rh- are at low risk of breast cancer. So, physicians should carefully monitor the females with blood group (A) and Rh+ as these females are more prone to develop breast cancer. To reduce the prevalence of the breast cancer and its burden, screening, and preventive programs for breast cancer especially in young women are highly recommended. Further studies are necessary to determine the mechanisms by which ABO blood type may influence the risk of breast cancer.

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The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

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The Relationship between ABO Blood Groups, Rhesus Factor and Breast Cancer

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