

# Relationship Between ABO Blood Group and the Risk of Colorectal Cancer: A Retrospective Multicenter Study

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## Abstract

**Background:** Colorectal cancer (CRC) is the fourth deadliest cancer, with approximately 900,000 deaths annually. CRC is a multifactorial disease in which a set of factors, including environmental, hereditary, and genetic factors, are integrated into cancer development. Studies have suggested an association between hereditary antigens in the human blood group system and the risk of different cancers. This study aimed to evaluate the relationship between blood groups and CRC risk.

**Methods:** A record-based retrospective study was performed between January 2017 and August 2021. This study targeted patients diagnosed with CRC during the study period. Data of patients who agreed to participate were collected using a pre-structured checklist. The extracted data included patients' demographic blood groups and risk factors, including history of inflammatory bowel disease or CRC.

**Results:** A total of 199 patients, aged 22 to 96 years (mean age: 61.6 ± 14.7 years), were included. The blood groups of 101 (50.8%), 59 (29.6%), 26 (13.1%), and 13 (6.5%) patients were O, A, B, and AB, respectively. Colon cancer was the most frequently reported cancer (155/199, 77.9%) across all blood groups and showed the highest frequency among patients with blood group O (74/155, 47.7%), without statistical significance ( $P = 0.111$ ).

**Conclusion:** Our study showed a statistically significant relationship between AB and non-O blood types and colon cancer compared to the O blood group.

**Keywords:** Blood group antigens; Colorectal neoplasms; Risk factors; Demography

## Introduction

Colorectal cancer (CRC) is the fourth deadliest cancer, with approximately 900,000 deaths annually [1]. In Saudi Arabia, CRC is the second most common malignancy [2], with a higher incidence among men and older adults [3-5]. CRC is a multifactorial disease in which a set of factors, including environmental, hereditary, and genetic factors, are integrated for cancer development [6, 7]. The etiology of colon and rectal cancers is not fully understood [8-10]. However, genetic factors and genetic abnormalities are known to play a role, especially at a young age [11-13].

Blood group antigens on the erythrocyte membrane are molecular structures, but they are also found in several epithelial cells, including the gastrointestinal mucosa. The ABO blood group system consists of antigens (A, B, O, and AB) [14]. Studies have suggested an association between hereditary antigens in the human blood group system and the risk of developing various cancers [15]. In 1993, Aird et al reported a relationship between the blood group and stomach cancer [16]. Recently, an association between the non-O serotype of the blood group and the risk of pancreatic cancer was reported [17]. In addition, numerous cancer cells express blood group antigens on the cell surface. Many studies have reported cancer-related changes in ABO antigen expression in human colon cancer tissues [18, 19].

Since few studies have assessed the association between ABO blood groups and CRC risk, the current study aimed to assess the relationship between ABO blood group and clinically significant parameters for CRC, such as grade, histopathological stage, and other clinicopathological factors.

## Materials and Methods

### Patients and data collection

A record-based retrospective study targeted patients diagnosed with CRC at Alhada Armed Forces Hospital, King Abdulaziz Specialist Hospital, and King Faisal Medical Complex in Taif, Saudi Arabia, from January 2017 to August 2021. The inclusion criteria were patients older than 15 years with a positive biopsy result for colorectal adenocarcinoma. In addition, patients younger than 15 years or with missing clinical data within medical files, patients with benign colorectal diseases,

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synchronous primary cancer, and non-adenocarcinoma CRCs were excluded. The data were collected from files of patients who met the inclusion criteria and agreed to participate using the pre-structured checklist (datasheet) to avoid data extraction errors. The extracted data included patient demographics (e.g., age, sex, and body mass index (BMI)), comorbidities, history of cancer or inflammatory bowel disease, blood grouping, location, differentiation of cancer, type of screening modality, and physical and dietary habits of participants. This study was approved by the Institutional Review Board of the Ethics Committee of the College of Medicine, Taif University, Saudi Arabia (H-02-T-078), and conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

### Assessment of ABO blood group and covariates

The included patients were divided into four groups according to their blood group type (A, B, AB, or O). If serologically was not reported, they were asked about their blood type and Rh factor (positive or negative). Data for the other covariates in this analysis were obtained from the patients' files. We used BMI (weight in kilograms/(height in meters)<sup>2</sup>) to measure total adiposity. In addition, participants were asked about their smoking status, history of inflammatory bowel disease, or family history of cancer (either yes or no). Participants were also asked about their intensity of physical activity (low, moderate, or high) and dietary usage per week (0 - 1, 2 - 4, or  $\geq 5$  servings per week). Clinicopathological factors such as histopathological grade (well, moderate, poor, mucinous, or undifferentiated), location of cancer (colon, rectum, or metastatic), and modality used for cancer diagnosis (colonoscopy, computed tomography (CT), guaiac-based fecal occult blood test (gFOBT), or sigmoidoscopy) were also obtained.

### Data analyses

The extracted data were revised, coded, and entered into the statistical software IBM SPSS version 22 (SPSS, Inc., Chicago, IL). All statistical analyses were performed using two-tailed tests. Statistical significance was set at  $P < 0.05$ . The distribution of different bio-demographic data, clinical and family history, clinical diagnosis of cancer type, and related screening methods were assessed by cross-tabulation analysis with patients' blood groups. Relationships were tested using the Pearson Chi-square test and the exact probability test for small frequency distributions. Cox proportional hazards models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all types of colon cancer.

## Results

A total of 199 patients were included, ranging from 22 to 96 years, with a mean age of  $61.6 \pm 14.7$  years old, 103 (51.8%) were men, 96 (48.2%) were women, and 59.3% were over-

weight and obese. Overall, 101 (50.8%), 59 (29.6%), 26 (13.1%), and 13 (6.5%) patients had blood groups O, A, B, and AB, respectively.

### Bio-demographic characteristics

There was no significant difference in ABO blood group bio-demographic characteristics of study participants according to age, sex, BMI, Rh factor, and medical history. However, there was a statistically significant finding in the history of cancer distribution, where 50% of those with blood group O had a history of cancer compared to 20.6%, 11.8%, and 17.6% of those with blood group A, B, and AB, respectively ( $P = 0.030$ ) (Table 1).

### Clinicopathological factors and ABO blood groups

Colon cancer is the most reported diagnosis among all blood groups. It was diagnosed in 155 (77.9%) patients, and the highest frequency was observed among those with blood group O (74 patients, 47.7%), without any statistical significance ( $P = 0.111$ ). Moderately differentiated adenocarcinoma was found among 150 (75.4%) histopathology results, 50% of patients with blood group O compared to 32%, 15.3%, and 2.7% of blood groups A, B, and AB, respectively ( $P = 0.003$ ). Regarding screening, 141 (70.9%) patients had no prior screening compared to 58 (29.1%) patients ( $P = 0.364$ ). Regarding the type of screening, 51 (87.9%) of the 58 patients underwent colonoscopic screening ( $P = 0.067$ ) (Table 2).

### Lifestyle factors and ABO blood groups

There was no significant difference among study participants in their physical activity or dietary habits according to blood group distribution except for red meat consumption, where the highest frequency of intake was in those with O blood group (55.6% use  $\geq 5$  servings per week) and the lowest frequency in those with A blood group (none had  $\geq 5$  servings per week;  $P = 0.037$ ) (Table 3).

### CRC and ABO blood groups

The risk of developing CRC according to ABO blood group type was not significantly different between the different ABO blood groups. Compared with blood group O, only a statistically significant association with colon cancer was observed in blood groups AB and non-O in the age-adjusted and multivariate-adjusted models. However, there was no statistically significant risk associated with any blood group for rectal cancer (Table 4).

## Discussion

The current study assessed the relationship between ABO

**Table 1.** Bio-Demographic Characteristics of Study Participants According to ABO Blood Group Type

Bio-demographic data	Total		Blood group								P-value
			A group		B group		AB group		O group		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Age in years											0.114
< 50	39	19.6%	10	25.6%	6	15.4%	2	5.1%	21	53.8%	
50 - 59	50	25.1%	18	36.0%	9	18.0%	1	2.0%	22	44.0%	
60 - 69	40	20.1%	10	25.0%	0	0.0%	3	7.5%	27	67.5%	
70+	70	35.2%	21	30.0%	11	15.7%	7	10.0%	31	44.3%	
Gender											0.880
Male	103	51.8%	33	32.0%	13	12.6%	7	6.8%	50	48.5%	
Female	96	48.2%	26	27.1%	13	13.5%	6	6.3%	51	53.1%	
Body mass index											0.357
Normal	81	40.7%	21	25.9%	13	16.0%	5	6.2%	42	51.9%	
Overweight	72	36.2%	18	25.0%	8	11.1%	5	6.9%	41	56.9%	
Obese	46	23.1%	20	43.5%	5	10.9%	3	6.5%	18	39.1%	
Rhesus factor (Rh factor)											0.631 <sup>a</sup>
Positive	184	92.5%	55	29.9%	25	13.6%	11	6.0%	93	50.5%	
Negative	15	7.5%	4	26.7%	1	6.7%	2	13.3%	8	53.3%	
Co-morbidities	118	59.3%	41	34.7%	15	12.7%	9	7.6%	53	44.9%	0.168
Smoking	5	2.5%	1	20.0%	1	20.0%	0	0.0%	3	60.0%	0.865 <sup>a</sup>
History of cancer	34	17.1%	7	20.6%	4	11.8%	6	17.6%	17	50.0%	0.030* <sup>a</sup>
History of hepatitis	8	4.0%	1	12.5%	0	0.0%	0	0.0%	7	87.5%	0.197 <sup>a</sup>
History of inflammatory bowel disease	2	1.0%	1	50.0%	1	50.0%	0	0.0%	0	0.0%	0.314 <sup>a</sup>
Family history of colorectal cancer	6	3.0%	1	16.7%	0	0.0%	0	0.0%	5	83.3%	0.408 <sup>a</sup>
History of hormone therapy	8	4.0%	2	25.0%	0	0.0%	0	0.0%	6	75.0%	0.447 <sup>a</sup>

P: Pearson  $\chi^2$  test. <sup>a</sup>Exact probability test. \*P < 0.05 (significant).

blood groups and CRC risk. A recent study suggested a possible association between ABO blood groups and the likelihood of having CRC [20]. Blood group antigens are present on the outer layer of erythrocytes and other tissues, such as epithelial cells of the gastrointestinal tract. The glycoconjugates in the ABO blood group antigens may play a role in changing intercellular adhesion, membrane signalling, and immune surveillance, which could influence tumorigenesis [21]. In addition, new genome-wide association studies have reported an association between single nucleotide polymorphisms in the ABO blood group with circulating levels of tumor necrosis factor- $\alpha$  and diabetes mellitus [22, 23]. Further, colorectal neoplasia is associated with the inflammatory marker, tumor necrosis factor- $\alpha$  [24].

The current study showed no significant difference between the patients' demographic characteristics and ABO blood group distribution. The only reported difference was among patients with a history of cancer in total, which may be explained by glycoconjugates modifying intercellular adhesion and membrane signaling with higher tumorigenesis [25]. In addition, there was no significant difference among patients' blood groups according to their dietary habits except for red

meat consumption, which was higher among those with blood group O.

Regarding the association between the ABO blood group and CRC, the current study showed no association between ABO and CRC diagnosis, where colon cancer was the most diagnosed among all types of blood groups. In addition, moderately differentiated cancers were the most reported among all types of ABO blood group, with the lowest rate among those with AB blood group and highest among those with blood group O (P = 0.003). The lack of association between ABO blood groups and CRC was also reported by Khalili et al, who found no significant association between blood group B and the overall risk of colon cancer [15]. In addition, no solid biological link may clarify the differential association between group B and group A antigens with cancer.

Conversely, Kashfi et al reported a significant relationship between blood group and colon cancer (P < 0.05), and the highest rate of colon cancer was reported among those with blood group O+ (48.7%), Rh+ (90.4%), and male patients (60.4%) [26]. Urun et al reported that ABO/Rh blood groups were significantly associated with CRC risk and that there was no relationship between K-ras status and the ABO blood group

**Table 2.** Cancer-Related Data Among Study Participants According to ABO Blood Group Type

Cancer data	Total		Blood group								P-value
			A group		B group		AB group		O group		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Diagnosis											0.111 <sup>a</sup>
Colon	155	77.9%	46	29.7%	23	14.8%	12	7.7%	74	47.7%	
Rectal	41	20.6%	13	31.7%	3	7.3%	0	0.0%	25	61.0%	
Metastasis	3	1.5%	0	0.0%	0	0.0%	1	33.3%	2	66.7%	
Differentiation											0.003 <sup>*a</sup>
Well	13	6.5%	3	23.1%	1	7.7%	3	23.1%	6	46.2%	
Moderate	150	75.4%	48	32.0%	23	15.3%	4	2.7%	75	50.0%	
Poor or mucinous	12	6.0%	3	25.0%	0	0.0%	2	16.7%	7	58.3%	
Undifferentiated	7	3.5%	1	14.3%	0	0.0%	3	42.9%	3	42.9%	
Unspecified	17	8.5%	4	23.5%	2	11.8%	1	5.9%	10	58.8%	
Screening											0.364
No	141	70.9%	38	27.0%	18	12.8%	8	5.7%	77	54.6%	
Yes	58	29.1%	21	36.2%	8	13.8%	5	8.6%	24	41.4%	
Type of screening											0.067 <sup>a</sup>
Colonoscopy	51	87.9%	21	41.2%	7	13.7%	3	5.9%	20	39.2%	
Sigmoidoscopy	5	8.6%	0	0.0%	1	20.0%	1	20.0%	3	60.0%	

P: Pearson X<sup>2</sup> test. <sup>a</sup>Exact probability test. \*P < 0.05 (significant).

**Table 3.** Physical and Dietary Habits Among Study Participants According to ABO Blood Group Type

Physical and dietary habits	Total		Blood group								P-value
			A group		B group		AB group		O group		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Physical activity											0.577
Low	98	49.2%	25	25.5%	14	14.3%	8	8.2%	51	52.0%	
Moderate	96	48.2%	32	33.3%	12	12.5%	4	4.2%	48	50.0%	
High	5	2.5%	2	40.0%	0	0.0%	1	20.0%	2	40.0%	
Processed meat usage											0.156
0 - 1 serving/week	137	68.8%	40	29.2%	19	13.9%	8	5.8%	70	51.1%	
2 - 4 servings/week	56	28.1%	19	33.9%	6	10.7%	3	5.4%	28	50.0%	
≥ 5 servings/week	6	3.0%	0	0.0%	1	16.7%	2	33.3%	3	50.0%	
Red meat usage											0.037 <sup>*</sup>
0 - 1 serving/week	103	51.8%	31	30.1%	14	13.6%	6	5.8%	52	50.5%	
2 - 4 servings/week	87	43.7%	28	32.2%	11	12.6%	4	4.6%	44	50.6%	
≥ 5 servings/week	9	4.5%	0	0.0%	1	11.1%	3	33.3%	5	55.6%	
Fruits usage											0.598
0 - 1 serving/week	111	55.8%	30	27.0%	17	15.3%	8	7.2%	56	50.5%	
2 - 4 servings/week	76	38.2%	25	32.9%	8	10.5%	3	3.9%	40	52.6%	
≥ 5 servings/week	12	6.0%	4	33.3%	1	8.3%	2	16.7%	5	41.7%	
Vegetable's usage											0.668
0 - 1 serving/week	106	53.3%	29	27.4%	14	13.2%	8	7.5%	55	51.9%	
2 - 4 servings/week	83	41.7%	29	34.9%	11	13.3%	4	4.8%	39	47.0%	
≥ 5 servings/week	10	5.0%	1	10.0%	1	10.0%	1	10.0%	7	70.0%	

P: exact probability test. \*P < 0.05 (significant).

**Table 4.** Risk of Colon Cancer and Rectal Cancer According to ABO Blood Group Type

	Blood group				
	O	A	B	AB	Non-O <sup>a</sup>
<b>Cancer colon</b>					
No. of cases/No. of person-years	74/4,623	46/2,848	23/1,368	12/802	81/5,018
Age-adjusted HR (95% CI)	1	1.3 (0.59 - 2.7)	2.8 (0.78 - 5.61)	4.1 (1.3 - 9.4)*	1.7 (1.1 - 4.2)*
Multivariable-adjusted HR (95% CI) <sup>b</sup>	1	1.2 (0.53 - 2.8)	2.7 (0.72 - 5.9)	3.1 (1.5 - 10.5)*	1.8 (1.1 - 4.2)*
<b>Rectal cancer</b>					
No. of cases/No. of person-years	27/1,500	13/868	3/192	1/76	17/1,136
Age-adjusted HR (95% CI)	1	0.97 (0.37 - 1.7)	0.35 (0.10 - 1.3)	0.24 (0.03 - 1.9)	0.59 (0.29 - 1.17)
Multivariable-adjusted HR (95% CI) <sup>b</sup>	1	0.82 (0.36 - 1.9)	0.37 (0.10 - 1.4)	0.32 (0.4 - 2.8)	0.56 (0.26 - 1.18)

<sup>a</sup>The non-O category included individuals with blood groups A, B, and AB. Hazard ratios are compared to those of blood group O. <sup>b</sup>Adjusted for age, sex, family and medical history, screening, physical activity, and dietary habits. \*Significant hazard ratio compared with the O blood group. HR: hazard ratio; CI: confidence interval.

and Rh factor [20].

As for CRC distribution according to ABO blood group, compared with blood group O, the only statistically significant association with colon cancer was observed with blood group AB in age-adjusted models (HR was 4.1, blood group AB; and 1.7, non-O blood group). However, for the multivariate-adjusted model, the AB blood group showed a significantly higher risk than blood group O (HR = 3.1). In addition, the non-O group showed a significantly higher risk than the blood group O (HR = 1.8). Notwithstanding, they did not appear to be a statistically significant risk associated with any blood group for rectal cancer which might be owing to the small sample size.

The current study also showed that most patients had moderately differentiated adenocarcinoma, which may be prevalent in the study region. The findings are consistent with those of Al-Ahwal et al [27], who assessed the pattern of CRC at two hospitals in the western region of Saudi Arabia and found that CRC stages at presentation were as follows: stage 0 (2.7%), stage I (11.7%), stage II (23.4%), stage III (20.7%), and stage IV (22.5%), and the staging was unknown in 18.9% of the patients. The most common tumor grade was moderately differentiated (38.7%), followed by poorly differentiated (20.7%), and well-differentiated (19.8%). Moreover, it was consistent with the findings of Mansoor et al [28] regarding adenocarcinoma as the most reported type of CRC.

In addition, the current study revealed that more than 70% of patients had no prior history of CRC screening. However, the remaining 30% of patients underwent screening at least once in their lives, which was primarily diagnostic but not screening intent. This is one of the few studies that focused on the ABO blood group and its relationship with CRC. However, the sample size was small, with many incomplete clinical data in the patients' medical records. In addition, the study's retrospective nature weakens the causative relation evidence, with a preference for longitudinal studies to assess the precise relationships with no bias.

Although all these studies point to a relationship between blood groups and specific cancers, supporting the theory that blood groups may play a role in cancer incidence and preva-

lence. Currently, preventative approaches take precedence over treatment methods. Advances in genetics can assist in identifying the characteristics that predispose people to cancer.

In summary, the present study revealed a relationship between AB and non-O blood types and colon cancer compared to the O blood group in age-adjusted models and the multivariate-adjusted model. However, the biological mechanism is worthy of further investigation, which may provide new information explaining the biological behavior, incidence, and prognosis of malignant tumors. Furthermore, whether moderately differentiated tumors were the most common among all types of ABO blood groups in our region's colon cancer incidence warrants further investigation.

## Conclusion

The study findings showed a statistically significant relationship between AB and non-O blood types and colon cancer compared to the O blood group. Thus far, the literature has shown no conclusion regarding this relationship, with some studies showing significant relations and others failing to prove this association. Large-scale studies are essential for identifying the role of genetic risk factors, such as blood groups, in the incidence of CRC. Controlling many factors, including environmental risk factors, with health education programs and increasing CRC awareness in contrast to screening measures, can decrease its incidence and related morbidity and mortality rates.

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## Financial Disclosure

None to declare.

## Conflict of Interest

The authors have no potential conflict of interest (financial, professional, or personal), and no company has provided any financial arrangements for this study.

## Informed Consent

Informed consent was obtained from all the included patients.

## Author Contributions

Conceptualization and design: AAS and SAS; patient data and samples: RAO, MAS, and KAH; experiments, collection and assembly of data: AAS, SAS, and WAH; data analysis and interpretation: AAS and MAH; manuscript writing and editing: MAS, RAO and MAH; critical revision: AAS. All authors have read and agreed to the published version of the manuscript.

## Data Availability

The data supporting the findings of this study are available on request from the corresponding author.

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