RESEARCH ARTICLE

ABO and Rh Blood Groups and Risk of Colorectal Adenocarcinoma

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Abstract

Background: Previous studies have observed an association between ABO blood group and risk for certain gastrointestinal malignancies, including pancreatic and gastric cancer. However, it is unclear whether there is such an association with colorectal cancer (CRC). In this study, possible relationships between ABO blood groups and Rh factor and KRAS status in patients with CRC were investigated. Materials and Methods: In 1,620 patients with CRC, blood group and Rh factor were examined and compared with the control group of 3,022,883 healthy volunteer blood donors of the Turkish Red Crescent between 2004 and 2011. The relationship of blood groups with wild type K-ras status was also evaluated. Results: Overall distributions of ABO blood groups as well as Rh factor were comparable between patients (45% A, 7.2% AB, 16.4% B, 31.4% O, and 87.2% Rh+) and controls (42.2% A, 7.6% AB, 16.3% B, 33.9% O, and 87.7% Rh+) (p=0.099). However, there were statistically significant difference between patients and controls with respect to O vs. non O blood group (p=0.033) and marginally significant difference for A vs. non-A blood group (p=0.052). Among patients, the median age was 62 (range 17-97), 58.1% were male. There were no statistically significant differences respect to sex and K-ras status. Conclusion: In present study, the ABO/Rh blood groups were statistically significantly associated with the risk of CRC. There were no relationship between K-ras status and ABO blood group and Rh factor. However further studies with larger numbers of patients are needed to establish the role of blood groups and to define the mechanisms by which ABO blood type affect CRC.

Keywords: Colon cancer - ABO blood group - Rh factor - K-ras

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Introduction

Colorectal cancer (CRC) is the third common cancer in both women and men and responsible for approximately 10% of all cancers. It is the third most common cause of cancer-related mortality for men and fourth for women. For the year 2008 about 1.2 million cases and 600 thousand deaths are estimated worldwide (Jemal et al., 2011). Age, adenomatous polyps, smoking, inflammatory bowel disease and dietary factors are some of the risk factors. Various genetic factors related to familial cases of colon cancer were identified. Familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome are well known examples of hereditary risk factors. However, these genetic syndromes and other known risk factors account for only a small number of CRC cases. Predisposing factors for most patients are not clear.

Blood group antigens are chemical components on the erythrocyte membrane but they are also expressed in a variety of epithelial cells including gastrointestinal mucosa. The antigens of the ABO system are actually the first human genetic markers. ABO blood group genes are mapped at the chromosome 9, in which the genetic alteration is common in many cancers (Hosoi, 2008). The correlations of ABO blood groups and Rh either with benign or malignant diseases have been observed for a long time In 1953 Aird et al. reported such a relationship with stomach cancer (Aird et al., 1953). Recently a significant association between ABO blood groups and cancer of the pancreas was reported (Wolpin et al., 2009; Greer et al., 2010; Iodice et al., 2010). Additionally

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genome wide association study (GWAS) identified the contribution of genetic variation in the ABO locus of 9q34 to pancreatic carcinogenesis (Amundadottir et al., 2009). Such a significant relationship hasn't been identified for CRC (Aird et al., 1954; Khalili et al., 2011). Various cancer cells express blood group antigens on cell surface and in several studies cancer associated alterations of ABO antigen expression in human colon cancer tissues have been reported (Schoentag et al., 1987; Dabelsteen et al., 1988; Dahiya et al., 1989; Nakagoe et al., 2001). However the correlation of ABO antigen expression either on erythrocyte or tumor cell, and genetic factors in CRC patients has not been studied yet. In this study, we aimed to investigate a possible relationship between ABO - Rh blood groups factor and KRAS status in patients with CRC.

Materials and Methods

All patients who had CRC and treated between 2000-2011 at the Departments of Medical Oncology of Ankara University Faculty of Medicine, Ankara Numune Research and Educational Hospital and Dr. Abdurrahman Yurtaslan Research and Educational Hospital (Ankara, Turkey) with defined ABO blood type and Rh factor were included in our retrospective reviews of tumor registry records. We excluded patient with a history of other cancer. All patients had the pathologically confirmed CRC. A group of volunteer healthy donors of Turkish Red Crescent (General Directorate of Blood Services, Science and Technological Research Directorate) between 01.01.2004 and 27.10.2011 were identified as a control group. The relationship of ABO blood types and Rh factor with various factors such as age at diagnosis, sex and KRAS status (available for 167 patients) evaluated from 1,620 CRC patients. Patients classified according to antigen status as follow; O (blood group O) and non O (group A, B, and AB); A (group A and AB) and nonA (group B and O); B (group B and AB) and nonB (group A and O). We compared the distributions of ABO blood types (A vs. nonA, B vs. nonB, O vs. non O), Rh factors (positive vs. negative) among 1,620 patients and 3,022,883 healthy controls. Among CRC patients, differences between each of aforementioned ABO blood groups and Rh factors with respect to various factors were explored, respectively.

This study was approved by the Institutional Review Board of Ankara University Faculty of Medicine.

KRAS genotyping

Formalin-fixed paraffin-embedded (FFPE) tumor tissues of patients used for the KRAS genotyping. The tumor cell content of each sample was assessed by a pathologist (B.S) on a slide stained with hematoxylin and eosin. Genomic DNA was extracted from three 6-μm FFPE sections using the QIAamp® DNA FFPE Tissue kit (Qiagen), according to manufacturer's instructions.

Mutational analysis was performed by using the TheraScreen®: K-RAS Mutation Kit that identifies the seven most frequent somatic mutations located in codons 12 and 13 (35G>A; 35G>C; 35G>T; 34G>A; 34G>C; 34G>T and 38G>A). Samples were analyzed according to the manufacturer's protocol and by using Real-Time PCR System (Roche LightCycler® 480).

Table 1. ABO Blood Groups and Rh of Patients with CRC and Healthy Population

	CRC group		Control group	
	n	%	n	%
A+	627	38.7	1,121,702	37.1
A-	102	6.3	154,330	5.1
B+	242	14.9	434,143	14.3
B-	24	1.5	59,626	2.0
AB+	102	6.3	200,972	6.7
AB-	15	0.9	28,582	1.0
0+	441	27.2	894,210	29.5
0-	67	4.1	129,318	4.3
Total	1620	100.0	3,022,883	100.0

*n, number; CRC, colorectal carcinoma

Statistical analysis was carried out using the computer program Statistical Package for the Social Sciences 13.0 for Windows (SPSS, Inc, Chicago, IL, USA). Descriptive statistics as frequency (percent) or median (minimum-maximum) were calculated for all variables. A χ^2 test was used to detect statistical differences in proportions. Odds ratio and its confidence interval were also calculated. All tests were two-tailed and a p value of less than 0.05 was considered significant.

Results

Among patients, the median age was 62 (range 17-97), 58.1% were male. Overall distributions of ABO blood groups as well as Rh factor were comparable between patients (45% A, 7.2% AB, 16.4% B, 31.4% O, and 87.2% Rh+) and controls (42.2% A, 7.6% AB, 16.3% B, 33.9% O, and 87.7% Rh+) (p=0.099) (Table 1). However, there were statistically significant difference between patients and controls with respect to O vs. non O blood group (OR, 1.121; 95%CI, 1.009-1.245; p=0.033) and marginally significant difference for A vs. nonA blood group (OR, 1.101; 95%CI, 1-1.215; p=0.052). There were not statistically significant differences respect to age and sex.

KRAS was evaluated in 167 patients and one hundred ten (66%) had WT and 57 (34%) patients had mutant KRAS and ABO blood types weren't correlated with KRAS status (P=0.867). However there was marginally significant difference respect to Rh and KRAS status in patients. Patients with WT KRAS status had more Rh negative than with mutant KRAS (p=0.073). Though not statistically significant, patients with A antigen had more WT KRAS status than patients with other blood groups. In addition, KRAS status of male and female patients was similar (p=0.950).

Discussion

The human ABO genes are located in chromosome 9q34.1-q34.2. There are three main allele forms, A, B, and O (Hosoi, 2008). The primary gene products are glycosyltransferases. ABO blood groups are determined by carbohydrate moieties, A and B antigens, on the

extracellular surface of the red blood cell membranes and anti-A or anti-B antibodies in the serum. However, ABO antigens are also expressed on the surface of many other cells, like epithelial cells. Alterations on the cell surface carbohydrate structures such as ABH blood group antigens can change the cell-cell and cell-extracellular matrix interactions that might be important for tumor development (Dall'olio, 1996). Alteration of ABO/Lewis antigen is associated with malignant transformation in some neoplasm.

Nakagoe et al. (2001) examined immunohistochemically the expression of blood group ABO isoantigens and Lewis related carbohydrate antigens compared according to cellular characteristics of tumor. Their study revealed that isoantigen A and siayl Lex were associated with nonpolypoid growth-type (NPG-type) tumors and these tumors were more likely to develop lymph node metastases (Nakagoe et al., 2001).

Possible associations between ABO blood group and the risk of some epithelial malignancies, including pancreatic cancer and gastric cancer have been reported previously (Aird et al., 1953; Amundadottir et al., 2009; Wolpin et al., 2009; Greer et al., 2010; Iodice et al., 2010). Aird et al. (1953) reported a relationship between gastric cancer and ABO blood groups in the 1950s. The frequency of blood group A was greater and O was lower in patient with gastric cancer than normal population. The distribution of blood group A and O was 44.8% and 44.5% in patient with gastric cancer and 39.8% and 48.6% in control group respectively (Aird et al., 1953). After this study Aird et al. (1954) investigated blood groups relation to CRC, breast and bronchus but they showed no significant relation with ABO blood groups (Aird et al., 1954). Pancreatic cancer is another cancer that relationship of ABO blood group was reported. Wolpin et al. reported that risk of pancreatic cancer was higher in patient with non-O blood group (A, B, and AB) than O. They observed highest risk for participants with blood group B (Wolpin et al., 2009). Although Greer et al. (2010) reported that frequency of blood group O was lower in patient with pancreatic cancer, in their study there were limited patient with blood group B and the frequency of blood group A was statistically significantly higher than normal population (Greer et al., 2010). Likewise Iodice et al. (2010) reported that O blood group was associated with a 47% risk reduction of pancreatic cancer but they didn't observe differences in the distribution of A versus non-A in patient with gastric cancer and CRC (Iodice et al., 2010). However population based cohort study of Edgren et al. has confirmed the association between blood group A and gastric cancer (Edgren et al., 2010).

Nevertheless, no consistent relationship between ABO blood type and CRC has been reported so far. Khalili et al. (2011) were examined the relationship between ABO blood groups and CRC in prospective cohort studies but they did not observe statistically significant association (Khalili et al., 2011). In the present study, statistically significant association was observed with non O blood group and marginally significant difference withblood group A and risk of CRC. Although these finding contrast with study of Khalili et al. (2011) it was consistent with study of Wolpin and Iodice (Wolpin et al., 2009; Iodice et al., 2010; Khalili et al., 2011).

KRAS (Kirsten rat sarcoma) is a proto-oncogene which is located on chromosome 12 and encoding protein that involved in normal cell proliferation and signal transduction. Mutations of the KRAS, especially in codon 12 or 13, have been reported in almost half of the CRC patient. To our knowledge, this is the first analysis of ABO blood group and KRAS in patient with CRC. In our study, we didn't find any relationship between KRAS status and ABO blood group and Rh factor.

In summary, the current study revealed that non O blood group was associated with risk of CRC. Nonetheless, further researches with larger number of patients are necessary to define the mechanisms by which ABO blood type may influence CRC risk and may clarify the role of blood groups in this population.

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