

ABO HISTO-BLOOD GROUPS AND RH SYSTEMS IN RELATION TO MALIGNANT TUMORS OF THE DIGESTIVE TRACT IN BOSNIA AND HERZEGOVINA

SNEŽANA JOVANOVIĆ-ĆUPIĆ¹, GORANA STAMENKOVIĆ², JELENA BLAGOJEVIĆ²,
N. VANIS³, B. STANOJEVIĆ¹, LJ. BERBEROVIĆ⁴

¹Laboratory of Radiobiology and Molecular Genetics, Vinča Institute for Nuclear Sciences, 11000 Belgrade, Serbia

²Siniša Stanković Institute for Biological Research, 11000 Belgrade, Serbia

³Gastroenterohepatology Clinic, Clinical Center, University of Sarajevo, 71000 Sarajevo, Bosnia and Herzegovina

⁴Faculty of Science, University of Sarajevo, 71000 Sarajevo, Bosnia and Herzegovina

Abstract — The distribution of ABO blood groups and the Rhesus factor was analyzed in 279 patients who suffered from malignant tumors of the digestive system. Patients were registered retrospectively in the Gastroenterohepatology Clinic, Clinical Center, University of Sarajevo over a discontinuous period of 88 months. From the results obtained, it was concluded that: (a) men became ill from gastric cancer significantly more frequently than women; (b) the frequency of liver carcinoma was three times higher than the global frequency and the frequency neighboring ethnic groups; and (c) patients with blood group B and patients with RhD(-) exhibited a significantly higher proportion of disease.

Key words: ABO blood groups, Rh systems, digestive system, malignant tumors, Bosnia and Herzegovina

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INTRODUCTION

Digestive cancers are the most common malignant tumors worldwide, with three million new cases each year (30% of all cancers). The incidence of digestive cancers is constantly increasing, mainly due to trends in colorectal cancer. Epidemiologists have suggested that the environment (including lifestyle factors) might play a profound role in maybe as many as 75% of all malignant tumors. There are striking variations in the risk of developing different cancers between geographic areas. Most of the international variation is due to exposure to known or suspected risk factors related to lifestyle or environment, and this provides a clear challenge in the field of prevention (Parkin et al., 2002).

Nevertheless, there is convincing evidence of genetic predisposition for different malignant diseases. While this is mainly related to polymorphism of tumor susceptibility genes – oncogenes and tumor suppressor genes – many investigations point to the significance of variability in genes whose indirect

products can affect the risk of appearance of certain types of tumors, products such as blood group antigens in man (Hakomori, 1999; Le Pendu et al., 2001; Fijneman, 2005). Polymorphism of blood groups in human populations has been investigated in correlation with the appearance of certain types of tumors, the degree of malignancy, the response to therapy and survival (Hakomori, 1999; Le Pendu et al., 2001). Most studies in this field are devoted to the ABH and RH antigen systems, which are known to be the most immunogenic and polymorphic human antigens.

Isoantigens of the human ABH system are represented by a variety of glycoproteins and glycolipids, the antigenic specificity of which is determined by variation in their constituent carbohydrate chains. These determinants are expressed on red blood cells, endothelial cells, and many normal epithelial cells, with wide spectra of different functions in cell physiology, fractions such as management of the structural integrity of membranes, cell adhesion,

and involvement in transfer of information among cells. The expression pattern of ABH antigens drastically changes during normal cell development and during neoplastic cell differentiation (Okada et al., 1987; Ishikawa et al., 1998; Nakagoe et al., 2001). Also, previous investigations have shown a higher incidence of various types of carcinomas in individuals with blood groups A and B compared with those with blood group O (Beckman and Angqvist, 1987; Slater et al., 1993; Kokić et al., 1996; You et al., 2000; Su et al., 2001; Guleria et al., 2005).

Contrary to ABH histo-blood antigens, Rh antigens include very complex transmembrane proteins, so-called trimers composed of RhD/CcEe proteins and Rh-associated glycoproteins (RhAG), detected on erythrocyte membranes only. Recent investigations showed that Rh protein complexes could have a role as NH₃ and CO₂ transporters in mammals, placing them among the most significant key structural and functional molecules on erythrocyte membranes (Kurstu and Inwood, 2006). However, it is still not clear how the RhD (-) phenotype, in which synthesis of RhD protein is absent, could affect pathological processes of tumorigenesis. Rare investigations of the effect of Rh status on the appearance of different types of tumors, as well as the degree of survival, have provided no congruent results (Halvorsen, 1986; Bryne et al., 1991; Slater et al., 1993; Manzoni et al., 2001).

The distribution of ABO and Rh blood groups varies geographically due to selection pressures and significant migrations of human populations (www.bloodbook.com/world-abo.html). On Eurasian land, the frequency of phenotype A increases from East to West, while the frequency of phenotype B has the opposite trend. Thus, in East Asian countries (Japan, China, and India) the occurrence of blood group B is about 40%, while blood group A is present in frequencies of 20 to 30%. In contrast, in Europe the frequency of blood group A is the highest (about 40%) while blood group B is present in 10 to 20% of the population [highest in Russia (23%), lowest in Scandinavia (10%)]. Blood group O has a frequency of about 40%, with minor variations (www.bloodbook.com/world-abo.html). Migrations on the

Balkan Peninsula were significant during the past century, particularly in Bosnia and Herzegovina, which resulted in different frequencies of ABO and Rh genotypes and phenotypes in comparison with the neighborhood (Bošković, 1966, 1975).

In the last decade, numerous results were obtained which make clearer different functions of human blood groups and the biological meaning of their polymorphisms in normal and pathogenic cells (Hacomori, 1999; Van Kim et al., 2006). Investigations on the predisposition for appearance of certain types of malignancies in relation to the ABH/Rh isoantigen systems have made a significant contribution to resolving these phenomena (Bryne et al., 1981; Halvorsen, 1986; Slater et al., 1993; Su et al., 2001; Guleria et al., 2005).

The main aim of this investigation was to ascertain whether there is any relationship between the appearance of certain types of tumors in the digestive tract and the ABO/Rh systems in a population from Bosnia and Herzegovina. In addition, we compared our results with those obtained for other populations in order to explore the possible influences of genetic background on these types of associations.

PATIENTS AND METHODS

Three hundred and fifty patients were registered retrospectively in the Gastroenterohepatology Clinic, Clinical Center, University of Sarajevo over a discontinuous period of 88 months (1987, 1988, September 1992 – December 1995, 1997, and 1998). Seventy-one cases were excluded from the study because the clinical evidence was not complete, so the total number of analyzed patients was 279. The following clinical data for each patient were included: sex, age, blood group (A, B, AB, O), Rh factor (D +/-), and localization of the primary tumor in the digestive tract (esophagus - EC, gastric - GC, duodenum - DC, colon - CC, rectum - RC, and liver - LC).

Statistical analyses

The differences in ABO/Rh blood group distribution in patient groups and the general population of Bosnia and Herzegovina (Bošković, 1965, 1975) as the control were assessed using the

Chi-square test. Student's t-test was used to compare average age values between sexes. Data were stored in a computer database and analyzed using Statistica 6.0 software.

RESULTS

The average age of the studied patients with malignant tumors of the digestive system was 59.5 years (range 3-90 years). There were no differences in mean age between the sexes (t = 0.08, n.s.). The incidence of digestive system cancer increased with age, beginning at 30 years but remained relatively low until the age of 50 years, after which it rapidly accelerated. The prevalence appeared to double with each successive decade until about the age of 70 years. One fifth of the analyzed group was younger than 50 years.

In general, significantly more men (59.9%) than women (40.1%) suffered from malignant tumors of the digestive system ($\chi^2 = 10.84$; df = 1; p<0.001). The main reason was the prevalence of GC and LC among men. The frequency of GC was twice as high in men as in women ($\chi^2 = 7.11$; df = 1; p< 0.01). In the case of LC, the overall sex ratio (male:female) was around 1.5 in the analyzed group of patients (Table 1).

The distribution of ABO blood groups in the studied group was not significantly different from that of the general population of Bosnia and Herzegovina ($\chi^2 = 5.40$, df = 3, p = 0.14). However, blood group B showed a significantly higher frequency in the studied group (17.9%) than in the general population (14.3%, Table 2).

There was no significant difference in the overall distribution of ABO blood groups between the anatomic localizations of digestive system tumors.

The Chi-square test showed that men with the B/Rh(-) blood type became ill significantly more often than expected in relation to the general population ($\chi^2 = 19.45$, df = 1, p<0.001). A similar trend was obtained in female patients, where women with A/Rh(+) became ill more rarely than expected ($\chi^2 = 4.29$, df = 1, p<0.05).

Generally, the distribution of RhD phenotypes regarding tumor localization was not significantly different from that expected.

DISCUSSION

Comparing the obtained results with global cancer statistics on tumors in the digestive tract, we see that our population of patients had a similar gender ratio with a higher number of males and a similar average age with a rapid increase after 50 years old (Ashly, 1990; Parkin et al., 2002).

Among the patients with malignancy in their digestive organs, we found the highest incidence of gastric cancer (38.35%). The incidence of LC and IC (duodenum, colon, and rectum) was approximately the same (27%, Table 1). This frequency of IC is half of the global frequency recorded in the population-based cancer registry (<http://www.iarc.fr>). In addition, the frequency of IC in neighboring ethnic groups in the former Yugoslav Republics ranged from 55 to 61% of the analyzed types of tumors of the digestive system (<http://www.iarc.fr>). On the other hand, the frequency of LC in our population

Table 1. Localization of malignant tumors in the digestive system in the examined group of patients (* p < 0.05, ** p < 0.01).

Localization of primary tumors	Men (% of this sex)	Women (% of this sex)	All (% of total)
Esophagus	9 (5.4)	7 (6.3)	16 (5.7)
Stomach	73 (43.7)**	34 (30.4)**	107 (38.4)
Duodenum	1 (0.6)	2 (1.8)	3 (1.1)
Colon	24 (14.4)	24 (21.4)	48 (17.2)
Rectum	14 (8.4)	14 (12.5)	28 (10.0)
Liver	46 (27.5)	31 (27.7)	77 (27.6)
All	167 (59.9)**	112(40.1) **	279

Table 2. Comparison of blood group frequency (ABO and Rh systems) in patients suffering from digestive tumors with frequencies in the wider population. (*data from Bošković, 1965, 1975; * $p < 0.05$, ** $p < 0.01$).

ABO blood groups	Men (% of this sex)	Women (% of this sex)	All (% of total)	Distribution in wider population (%)
Group A	73 (43.7)	47 (42.0)	120 (43.0)	(42.20)
Group B	32 (19.2)	18 (16.1)	50 (17.9)*	(14.34)
Group O	55 (32.9)	41 (36.6)	96 (34.4)	(36.18)
Group AB	7 (4.2)	6 (5.4)	13 (4.7)	(7.28)
Rhesus type				
Rh(+)	133 (79.6)	91 (81.3)	224(80.3)	(84.2)
Rh(-)	34 (20.4)	21 (18.8)	55 (19.7)*	(15.8)
All	167 (59.1)	112(40.9)	279	

was higher than the global frequency and the frequency in neighboring ethnic groups (up to 10% of the analyzed types of digestive system tumors in the former Yugoslav Republics, <http://www.iarc.fr>). In the last two decades, the frequency of LC has rapidly increased due to increase and change in the prevalence of risk factors (for example, a higher incidence of chronic viral hepatitis) as well as changes in diagnostic techniques and in classification of the disease (Yu et al., 2000; McGlynn and London, 2005).

The distribution of ABO blood groups in the studied group was not significantly different from that in the general population of Bosnia and Herzegovina, except for a significant difference in the frequency of patients with blood group B (Table 2). Most studies have shown that individuals with blood group A or B have a slightly higher probability of developing cancer of the digestive system than blood group O individuals (Annese et al., 1990; Slater et al., 1993; Pandey et al., 1995; You et al., 2000; Le Pendu et al., 2001; Su et al., 2001; Guleria et al., 2005).

The increased risk for developing cancers in individuals with blood group A may be attributable to expression of an „A-like antigen“ (also called the Forssmann or Tn antigen). So-called „incompatible A expression“ was detected in some types of gastric, liver, ovarian, colorectal and salivary gland cancer. Cancer cells of these tumors are capable of A antigen expression even in individuals with blood group B or O (Okada et al., 1987; Hakomori,

1999). Thus, antibodies to A can attack precancerous and cancerous cells expressing this antigen. Individuals with blood groups A and AB lack antibodies to A and so are more likely to develop these carcinomas (Beckman and Angqvist, 1987; Hakomori, 1999). According to other results, the protective effect of blood group O on cancer development can be ascribed to increased apoptosis resistance of epithelial cells presenting A and B antigens (Ichikawa et al., 1998, Le Pendu et al., 2001; Marionneau et al., 2002).

In our study group, we detected a significantly higher frequency of patients with the RhD(-) phenotype. Most authors have been unable to find any relationship between the Rh factor erythrocyte membrane system of proteins and human cancerogenesis (Mazoni et al., 2001). However, Halvorsen (1986) showed significant differences in stage distributions of colorectal adenocarcinoma in RhD(+) and RhD(-) patients. Slater et al. (1993) ascertained a significantly higher frequency of RhD(-) in groups of patients with colorectal tumors in early stages of development and with incurable tumors. Some research has suggested that the prognosis of survival for five years in RhD(+) patients is considerably better than in RhD(-) patients (Bryne et al., 1981).

The effect of Rh phenotype in some pathological processes may be connected with the physiological role of very different and complex proteins of the Rh system in the transport of toxic biological gases such as ammonia or carbon dioxide to detoxifying organs,

e. g. the liver or kidney (Van Kim et al., 2005; Kustu and Inwood, 2006). Also, association of the RhD(-) phenotype with a higher frequency of cancer could be related to linkage disequilibrium. To be specific, the Rh gene locus is located on the short arm of chromosome 1 (1p36.2-1p34), where some oncogenes are also located, but linkage analysis for these genes is still unclear (Ferrell et al., 1989; Rolfe et al., 2002).

The effect of the RhD(-) phenotype was higher in male patients with blood group B ($p < 0.01$). In contrast, females with phenotype A/RhD(+) became ill significantly less than expected ($p < 0.05$). Results showing important differences in the distribution of RhD phenotypes in relation to particular ABO blood groups are still rare and can depend on the examined malignancy and features of the investigated population. For example, in patients who suffered from pancreatic cancer, phenotype O/RhD(+) had a protective effect while AB/RhD(-) was a risk factor for endometrial carcinoma (Kokić et al., 1996; Adamian, 2005). Since ABO(H) blood group genes map at 9q and Rh system genes map at 1p, genetic linkage between these two groups of genes is excluded (Hakomori, 1999). On the other hand, the influence of gender on the appearance of digestive tumors with certain ABO/Rh status could issue from the very complex pathology of cancerogenesis, involving interactions of a huge number of environmental, physiological, and genetic factors (Kelley and Duggan, 2003; Fijneman, 2005).

Many reports have shown different associations of blood groups and the appearance of cancer based on geographical localization and ethnic qualifications (Pandey et al., 1995; You et al., 2000; Guleria et al., 2005). A protective effect for the O/Rh(+) phenotype was detected for pancreatic tumors in an ethnically close population in Serbia (Kokić et al., 1996). In addition, blood group B was detected as a risk factor in the appearance of anaplastic thyroid cancer in Serbia (Živaljević et al., 2008). However, besides genetic background, the complex etiology of tumorogenesis in the digestive organs includes many environmental factors, such as cigarette smoking, dietary practices, alcohol consumption, infectious diseases like viral hepatitis

or *Helicobacter pylori*, etc. (Kelley and Duggan, 2003; Yu et al., 2000). It follows that the effects of a particular genotype and/or phenotype, like the ABO/Rh system, should be investigated in more homogeneous groups in relation to the above-mentioned environmental risk factors (Yu et al., 2000; Kelley and Duggan, 2003).

In conclusion, it can be asserted that the ABO and Rhesus systems contributed to a predisposition for appearance of malignant tumors in the digestive organs of the population studied.

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КРВНЕ ГРУПЕ АВО И RH СИСТЕМА У УЗОРКУ ОБОЛЕЛИХ ОД МАЛИГНИХ ТУМОРА ДИГЕСТИВНОГ ТРАКТА У БОСНИ И ХЕРЦЕГОВИНИ

СНЕЖАНА ЈОВАНОВИЋ-ЂУПИЋ¹, ГОРАНА СТАМЕНКОВИЋ², ЈЕЛЕНА БЛАГОЈЕВИЋ²,
Н. ВАНИС³, Б. СТАНОЈЕВИЋ¹ и Љ. БЕРБЕРОВИЋ⁴

¹Институт за нуклеарне науке "Винча", 11000 Београд, Србија

²Институт за биолошка истраживања "Синиша Станковић", 11060 Београд, Србија

³Клинички центар Универзитета Сарајево, 71000 Сарајево, Босна и Херцеговина

⁴Универзитет у Сарајеву, 71000 Сарајево, Босна и Херцеговина

Анализирана је дистрибуција крвних група АВО система и Резус фактора код 279 пацијената оболелих од малигнух тумора дигестивног система. Пацијенти су регистровани ретроспективно у Гастроентерохепатолошкој клиници Клиничког центра Универзитета у Сарајеву у дисконтинуитету током 88 месеци (1987–1998). На основу анализираних популација пацијената закључено

је да: (а) мушкарци значајно чешће обољевају од канцера желуца у односу на жене; (б) учесталост карцинома јетре је три пута већа у поређењу са учесталостима овог обољења у свету и суседним земљама; (ц) пацијенти са В крвном групом и пацијенти са RhD(–) су у значајном степену чешћи у испитиваној популацији оболелих од очекиваног.