

RESEARCH ARTICLE

Lack of any Association between Blood Groups and Lung Cancer, Independent of Histology

Arzu Oguz^{1*}, Dilek Ünal², Arzu Taşdemir³, Samet Karahan⁴, Fatma Aykas⁴, Hasan Mutlu⁵, Yasemin Benderli Cihan⁶, Mehmet Kanbay⁷

Abstract

Introduction: Lung cancer, the leading cause of cancer deaths, is divided into 2 main classes based on its biology, therapy and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Many cases are at an advanced stage at diagnosis, which is a major obstacle to improving outcomes. It is important to define the high risk group patients for early diagnosis and chance of cure. Blood group antigens are chemical components on erythrocyte membranes but they are also expressed on a variety of epithelial cells. Links between ABO blood groups with benign or malignant diseases, such as gastric and pancreas cancers, have been observed for a long time. In this study, we aimed to investigate any possible relationship between lung cancer histological subtypes and ABO-Rh blood groups. **Materials and Methods:** The files of 307 pathologically confirmed lung cancer patients were reviewed retrospectively. Cases with a serologically determined blood group and Rh factor were included and those with a history of another primary cancer were excluded, leaving a total of 221. The distribution of blood groups of the lung cancer patients were compared with the distribution of blood groups of healthy donors admitted to the Turkish Red Crescent Blood Service in our city in the year 2012. **Results:** There was no significant difference between patients with lung cancer of either type and the control group in terms of distribution of ABO blood groups and Rh factor ($p: 0.073$). There was also no relationship with non small cell cancer histological subtypes. **Conclusions:** In this study, we found no relationship between the ABO-Rhesus blood groups and NSCLC and SCLC groups. To our knowledge this is the first analysis of ABO blood groups in SCLC patients.

Keywords: Lung cancer - ABO blood groups - Rh factor - SCLC - NSCLC - Turkey

Asian Pacific J Cancer Prev, 14 (1), 453-456

Introduction

Lung cancer is the leading cause of cancer deaths. It is divided into 2 classes based on its biology, therapy and prognosis as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), by the World Health Organization. NSCLC, accounting for more than 85% of all lung cancer cases, consists of two major histological subtypes; non-squamous (adeno, large cell and other cell types) and squamous. Only about 15.6% of all lung cancer cases are alive 5 years or more after diagnosis (Siegel et al., 2011). Much of the cases are at the advanced stage on diagnosis, so late diagnosis is still an obstacle to improving the outcomes in this malignancy and early stage at diagnosis is an important prognostic factor (Finkelstein et al., 1986). As screening and early diagnosis have been shown to increase survival in some solid tumors as breast, colon and cervix and since localized lung cancer can be managed curatively; it is believed that lung cancer is an appropriate candidate for population based screening

programs. In National Lung Screening Trial (NLST), it has been shown that screening high risk patients with low-dose helical CT decreases the mortality rate from lung cancer by 20% compared to chest x-ray. In that study, high risk patients were 55-74 years old and current or former smokers with a 30 pack-year smoking history (Aberle et al., 2011). So it is important to define the high risk group patients for early diagnosis and chance of cure.

The ABO blood group system was first discovered by Karl Landsteiner in 1900 (Landsteiner, 1900). Blood group antigens are chemical components on the erythrocyte membrane but they are also expressed on a variety of epithelial cells including urothelium, gastrointestinal, mucosa and lung as well as saliva and body fluids (Zmijewski, 1978; Graziano et al., 1997). ABO blood group genes are mapped at the chromosome 9q and consist of 7 exons, in which the genetic alteration is common in many cancers (Hosoi, 2008). The ABO gene encodes a glycosyltransferase catalyzing the transfer of carbohydrates to the H antigen, thus forming the antigenic

¹Medical Oncology Clinic, ²Radiation Oncology Clinic, ³Pathology Clinic, ⁴Internal Medicine Clinic, Kayseri Education and Research Hospital, ⁵Medical Oncology Clinic, ⁶Radiation Oncology Clinic, Acıbadem Hospital, ⁷Nephrology Clinic, Istanbul Medeniyet University, Istanbul, Turkey *For correspondence: e-mail oguzarzu@yahoo.com

structure of the ABO blood groups (Reid and Mohandas, 2004). The correlations of ABO blood groups either with benign or malignant diseases has been observed for a long time. In 1953 Aird et al. reported such a relation with gastric cancer. They have found that blood group A was significantly more frequent, while blood group O was less frequent in patients with gastric cancer when compared with normal population in England (Aird et al., 1953). Recently in some studies, 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, genome wide association studies (GWAS) among pancreatic cancer cases and controls have identified the contribution of genetic variation in the ABO locus of 9q34 to pancreatic carcinogenesis (Amundadottir et al., 2009). In some studies on early stage surgically treated lung cancer patients, it has been shown that loss of blood group antigen A is a negative prognostic factor (Graziano et al., 1997; Lee et al., 1991; Miyake et al., 1992). But still the correlation between lung cancer histological subtypes and ABO blood types, if any, is not clearly defined. In this study, we aimed to investigate any possible relationship.

Materials and Methods

The files of 307 lung cancer patients, who were confirmed pathologically, from 2009-2012 in the department of Medical Oncology at Kayseri Education and Research Hospital were evaluated retrospectively. The cases that have serologically determined blood group and Rh factor were included in the study and the ones with a history of another primary cancer were excluded. A total of 221 files were included in the study. Patients were classified according to blood groups (A, B, AB, O) and Rh status (+, -). The histopathological subtypes were recorded as small cell and non-small cell. For non small cell lung cancer cases, if the subtypes were determined as adeno, squamous or large cell type, they were also recorded. The relationship of blood groups with lung cancer subtypes was evaluated. The distribution of blood groups of the lung cancer patients were compared with the distribution of blood groups of healthy donors that admitted to the Turkish Red Crescent Blood Service in our city in year 2012.

SPSS 15.0 software (SPSSFW; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Qualitative variables are given as percent and the correlation between categorical variables was investigated using the chi-square test. A p value of <0.05 was considered significant.

Results

Table 1 shows comparison of ABO blood groups and Rh factor between patients with lung cancer and control group. There was no significant difference between patients with lung cancer and control group in terms of distribution of ABO blood groups and Rh factor (p: 0.073).

The percentages of lung cancer patients with A, B, AB and O blood groups were 43.9%, 13.6%, 9.0% and 33.5%, whereas those of control group were 44.8%, 16.3%, 7.6% and 31.3%, respectively. There was no significant

Table 1. Comparison of ABO Blood Groups and Rh Factor between Lung Cancer and Control Groups

	Lung cancer group	Control group
A Rh (+)	80 (36.2)	6811 (39.3)
A Rh (-)	17 (7.7)	945 (5.5)
B Rh (+)	26 (11.8)	2486 (14.4)
B Rh (-)	4 (1.8)	333 (1.9)
AB Rh (+)	13 (5.9)	1131 (6.5)
AB Rh (-)	7 (3.1)	185 (1.1)
O Rh (+)	64 (29.0)	4763 (27.5)
O Rh (-)	10 (4.5)	660 (3.8)
Total	221 (100)	17314 (100)

Table 2. Comparison of ABO Blood Groups and Rh Factor between Different Lung Cancer Types

	Small cell cancer n (%)	Adenocancer n (%)	Squamous cell cancer n (%)
A Rh (+)	18 (47.4)	15 (27.8)	29 (37.2)
A Rh (-)	2 (5.3)	3 (5.6)	7 (9.0)
B Rh (+)	2 (5.3)	6 (11.1)	12 (15.4)
B Rh (-)	-	-	2 (2.6)
AB Rh (+)	2 (5.3)	4 (7.4)	5 (6.4)
AB Rh (-)	1 (2.6)	2 (3.7)	3 (3.8)
O Rh (+)	10 (26.3)	21 (38.9)	18 (23.1)
O Rh (-)	3 (7.9)	3 (5.6)	2 (2.6)
Total	38 (100)	54 (100)	78 (100)

difference between lung cancer group and control group in terms of distribution of ABO blood groups (p: 0.583).

Table 2 shows comparison of ABO blood groups and Rh factor between different lung cancer types. There was no significant difference between different lung cancer types in terms of distribution of ABO blood groups and Rh factor (p: 0.563).

The percentages of A, B, AB, and O blood groups in patients with small cell cancer were 52.6%, 5.3%, 7.9%, and 34.2%, respectively. The percentages of A, B, AB, and O blood groups in patients with adenocancer were 33.3%, 11.1%, 11.1%, and 44.4%, whereas same percentages in patients with squamous cell cancer were 46.2%, 17.9%, 10.3%, and 25.6%, respectively. There was no significant difference between different lung cancer types in terms of distribution of ABO blood groups (p: 0.166).

Table 3 shows comparison of ABO blood groups and Rh factor between patients with small cell cancer and those with non-small cell cancer. There was no significant difference between patients with small cell cancer and those with non-small cell cancer in terms of distribution of ABO blood groups and Rh factor (p: 0.570). The percentages of A, B, AB, and O blood groups in patients with small cell cancer were 52.6%, 5.3%, 7.9%, and 34.2%, whereas the percentages of A, B, AB, and O blood groups in patients with non-small cell cancer were 42.1%, 15.3%, 9.3%, and 33.3%, respectively. There was no significant difference between patients with small cell cancer and those with non-small cell cancer in terms of distribution of ABO blood groups (p: 0.361).

Table 4 shows comparison of ABO blood groups and Rh factor between patients with different lung cancer types and control group. There was no significant difference

Table 3. Comparison of ABO Blood Groups and Rh Factor between Different Lung Cancer Types

	Small cell cancer n (%)	Non-small cell cancer n (%)
A Rh (+)	18 (47.4)	62 (33.9)
A Rh (-)	2 (5.3)	15 (8.2)
B Rh (+)	2 (5.3)	24 (13.1)
B Rh (-)	-	4 (2.2)
AB Rh (+)	2 (5.3)	11 (6.0)
AB Rh (-)	1 (2.6)	6 (3.3)
O Rh (+)	10 (26.3)	54 (29.5)
O Rh (-)	3 (7.9)	7 (3.8)
Total	38 (100)	183 (100)

Table 4. Comparison of ABO Blood Groups and Rh Factor between Patients with Different Lung Cancer Types and Control Group

	Small cell ca n (%)	Adeno ca n (%)	Squamous cell ca n (%)	Control n (%)
A Rh (+)	18 (47.4)	15 (27.8)	29 (37.2)	6811 (39.3)
A Rh (-)	2 (5.3)	3 (5.6)	7 (9.0)	945 (5.5)
B Rh (+)	2 (5.3)	6 (11.1)	12 (15.4)	2486 (14.4)
B Rh (-)	-	-	2 (2.6)	333 (1.9)
AB Rh (+)	2 (5.3)	4 (7.4)	5 (6.4)	1131 (6.5)
AB Rh (-)	1 (2.6)	2 (3.7)	3 (3.8)	185 (1.1)
O Rh (+)	10 (26.3)	21 (38.9)	18 (23.1)	4763 (27.5)
O Rh (-)	3 (7.9)	3 (5.6)	2 (2.6)	660 (3.8)
Total	38 (100)	54 (100)	78 (100)	17314 (100)

between patients with small cell lung cancer and control group in terms of distribution of ABO blood groups and Rh factor (p: 0.520). The percentages of small cell lung cancer patients with A, B, AB and O blood groups were 52.6%, 5.3%, 7.9% and 34.2%, whereas those of control group were 44.8%, 16.3%, 7.6% and 31.3%, respectively. There was no significant difference between small cell lung cancer group and control group in terms of distribution of ABO blood groups (p: 0.326).

There was no significant difference between patients with adeno lung cancer and control group in terms of distribution of ABO blood groups and Rh factor (p: 0.203). The percentages of adeno lung cancer patients with A, B, AB and O blood groups were 33.3%, 11.1%, 11.1% and 44.4%, respectively. There was no significant difference between adeno lung cancer group and control group in terms of distribution of ABO blood groups (p: 0.098).

There was no significant difference between patients with squamous cell lung cancer and control group in terms of distribution of ABO blood groups and Rh factor (p: 0.292). The percentages of squamous cell lung cancer patients with A, B, AB and O blood groups were 46.2%, 17.9%, 10.3%, and 25.6%, respectively. There was no significant difference between squamous cell lung cancer group and control group in terms of distribution of ABO blood groups (p: 0.640).

Although we do not present in a separate table, ABO blood groups and Rh factor in all patients with non-small cell cancer are shown in Table 3. On the other hand, same data in control group is shown in Table 4. There was no significant difference between patients with non-small cell lung cancer and control group in terms of distribution

of ABO blood groups and Rh factor (p: 0.084). The percentages of non-small cell lung cancer patients with A, B, AB and O blood groups were 42.1%, 15.3%, 9.3%, and 33.3%, respectively. There was no significant difference between non-small cell lung cancer group and control group in terms of distribution of ABO blood groups (p: 0.640).

Discussion

ABO antigens are expressed on the surface of many cells other than erythrocytes, like epithelial cells including urothelium, gastrointestinal, mucosa and lung. Alterations on the cell surface structures as blood group antigens, can lead to changes in the interactions in between cells or cells and extracellular matrix. These changes have been thought to be important for tumor development (Dall'olio, 1996). Possible associations between ABO blood group and risk of some epithelial malignancies, including gastric and pancreatic cancer have been reported previously. Aird et al reported that the frequency of blood group A was significantly higher (44.8% and 39.8% respectively in cancer cases and controls) and blood group O was significantly lower (44.5% and 48.6% respectively) in patients with gastric cancer than normal population (Aird et al., 1953). Edgren et al have established a cohort study on more than a million healthy blood donors using Scandinavian Donations and Transfusions database. After a follow up of 35 years, 688 newly diagnosed gastric cancer cases were detected. They have concluded that blood group A was associated with a higher risk of gastric cancer with an incident rate ratio of 1.20 (95% CI: 1.02-1.42) (Edgren et al., 2010).

Wolpin et al have examined the relationship between blood groups and the risk of pancreatic cancer in two prospective cohort studies. After a mean follow up of 8.6 years, 316 participants developed pancreatic cancer. They have stated that, the risk of developing pancreatic cancer differed significantly by blood group types. Those with blood group A, AB or B were more likely to develop pancreatic cancer compared with group O. The highest risk was for blood group B (Wolpin et al., 2009). In Amundadottir and colleagues' genome-wide association study among pancreatic cancer cases and controls, it was stated that single nucleotide polymorphisms at the ABO gene locus are the important associations with pancreatic cancer risk (Amundadottir et al., 2009). From this prospective cohort genotype data's, Wolpin et al evaluated individual ABO alleles and determined the association with pancreatic tumorigenesis. An increased risk was observed with the addition of each non-O allele. Also in combination with the best defined modifiable risk factors of pancreas cancer as smoking, overweight and diabetes; also the non-O blood group was associated with increased risk compared with O blood group (Wolpin et al., 2010). Iodice et al compared the distribution of ABO blood types in patients of each specific type of cancer with that of patients with other forms of cancer. They detected a significantly lower frequency of blood group O in exocrine pancreatic cancer group compared with other forms of cancer (29% vs 44%, p<0,001). For other organ cancers

there was no association detected (Iodice et al., 2010). Ürün et al (2012) compared blood group antigen and Rh factor levels in patients with gastrointestinal stromal tumor with normal population and concluded that a significant correlation was not present for gastrointestinal stromal tumor patients (p levels were 0,71 and 0,98 respectively).

The earliest data about lung cancer and ABO blood group relation belongs to Ashley. In the whole population, there was not a significant difference in blood group types compared to controls. But for tumor location, there was a significantly lower O group frequency in proximally located tumors than distal ones. For histological subtypes, the frequency of group O in undifferentiated subtype was higher than in squamous subtype. Also the frequency of group B was significantly higher in the glandular tumors than other two subtypes. There was no difference detected for Rhesus blood groups among all subtypes of patients (Ashley, 1969).

Roberts et al compared the ABO blood group frequencies in 86 resected lung cancer patients with normal controls. The overall frequencies were similar to controls, but those patients with blood group B or AB had a significantly shorter survival (24 and 14 months respectively) after operation than other blood groups (for A and O blood groups: 48 and 60 months respectively; p:0.0017) (Roberts et al., 1988).

Lee et al. studied the survival of operable nscLc patients according to blood groups. They found that survival was significantly shorter in patients with blood group A (p<0,001) (Lee et al., 1991). In another study, clinical course of nscLc patients was correlated with the staining of a monoclonal migration-inhibiting antibody. Since the survival of the patients were found to be significantly correlated with the staining of this antibody; it was suggested that, tumor associated carbohydrate antigens may be important for tumor invasiveness and metastatic potential in nscLc patients (Lee and Hong, 1992). By evaluating cell surface A antigen loss and flow cytometric analysis in 260 resected early stage nscLc patients, Graziano et al. stated that the median survival of patients with a primary tumor negative for blood group A antigen were significantly shorter than other groups (p<0,01). Aneuploidy and percentage of cells in S-phase were not found to be correlated with survival. The loss of antigen A was found to be one of the prognostic factors for survival in resected NSCLC patients (Graziano et al., 1997).

The impact of ABO blood types on lung cancer risk factors as tobacco use, high salt and fat intake, occupational dust exposure, alcohol intake, older age were also evaluated. Since in each blood group type, different lifestyle factors were found to be associated with lung cancer mortality; ABO type might affect the impact of different lifestyle factors (Suadicani et al., 2007).

In this study, we found no relationship between the ABO-Rhesus blood groups compared to control. To our knowledge this is the first analysis of ABO blood groups in SCLC patients. For NSCLC histological subtypes, there was not a significant difference detected for neither blood group analysis nor rhesus status. Prospective large cohort studies are needed to determine if blood groups are helpful in defining patients at risk for developing lung cancer.

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