RESEARCH ARTICLE

Association of ABO Blood Group and Risk of Lung Cancer in a Multicenter Study in Turkey

Yuksel Urun[1]*, Gungor Utkan[1], Ayten Kayi Cangir[2], Omur Berna Oksuzoglu[3,4], Nuriye Ozdemir[3,5], Derya Gokmen Oztuna[6], Gokhan Kocaman[2], Hasan Şenol Coşkun[3,7], Muhammet Ali Kaplan[3,8], Cabir Yuksel[2], Ahmet Demirkazik[1], Fikri Icli[1]

Abstract

Background: The ABO blood groups and Rh factor may affect the risk of lung cancer. Materials and Methods: We analyzed 2,044 lung cancer patients with serologically confirmed ABO/Rh blood group. A group of 3,022,883 healthy blood donors of Turkish Red Crescent was identified as a control group. We compared the distributions of ABO/Rh blood group between them. Results: The median age was 62 years (range: 17-90). There was a clear male predominance (84% vs. 16%). Overall distributions of ABO blood groups were significantly different between patients and controls (p=0.01). There were also significant differences between patients and controls with respect to Rh positive vs. Rh negative (p=0.04) and O vs. non-O (p=0.002). There were no statistically significant differences of blood groups with respect to sex, age, or histology. Conclusions: In the study population, ABO blood types were associated with the lung cancer. Having non-O blood type and Rh-negative feature increased the risk of lung cancer. However, further prospective studies are necessary to define the mechanisms by which ABO blood type may influence the lung cancer risk.

Keywords: ABO blood - group system - lung neoplasms - cancer - risk factors

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Introduction

Lung cancer is the second most common cancer in both women and men. Although responsible for less than 15% of all cancers, lung cancer is the leading cause of cancer death in the world for both men and women. For the year 2008, about 1.6 million new cases and 1.4 million deaths are estimated worldwide (Jemal et al., 2011). Smoking is the most common risk factor for lung cancer (Dela Cruz et al., 2011). Nonetheless, 10-25% of lung cancer develops in never smokers. Exposure to environmental tobacco smoke, workplace carcinogens, ionizing radiation, and a number of genetic lesions and inherited predisposition are the other suggested potential risk factors for development of the lung cancer (Couraud et al., 2012).

The blood group antigens are actually the first human genetic markers. ABO blood group gene is mapped at the chromosome 9q34, in which the genetic alterations are common (Humphray et al., 2004). The correlation of ABO blood groups with certain disease including infections, vascular, and malignant diseases has been shown (Hakomori, 2001). ABO/Rh blood group was associated with increased risk of malignancies such as, gastric, pancreatic, ovarian, colorectal and kidney cancer (Wolpin et al., 2009; Edgren et al., 2010; Joh et al., 2012; Poole et al., 2012; Urun et al., 2012). However, the data on the role of ABO blood group and Rh factor in lung cancer is limited and inconsistent (Alvarez-Fernandez and Carretero-Albinana, 1991; Lee et al., 1991; Cerny et al., 1992; Miyake et al., 1992; Gwin et al., 1994; Rice et al., 1995; Graziano et al., 1997; Ulger et al., 2002; Sanchez-Mora et al., 2007; Suadicani et al., 2007; Leon-Atance et al., 2012).

The purpose of this study was to investigate a possible relationship between ABO/Rh blood groups and lung cancer and clinicopathologic features of lung cancer.

Materials and Methods

All patients who had pathologically confirmed diagnosis of lung cancer between 2000 and 2011 at the involved centers with serologically confirmed ABO/Rh were included in our retrospective reviews of tumor registry records. Volunteer healthy blood donors (ages 18

*[1]Department of Medical Oncology, [2]Department of Thoracic Surgery, [6]Department of Biostatistics, Ankara University School of Medicine, [3]Department of Medical Oncology, [4]Ankara Oncology Training and Research Hospital, [5]Ankara Numune Research and Educational Hospital, [7]Department of Medical Oncology, Akdeniz University Faculty of Medicine, [8]Department of Medical Oncology, Dicle University Faculty of Medicine, Turkey *For correspondence: yukselurun@gmail.com*

Table 1. ABO Blood Group and Rh Factor by Patient with Lung Cancer and Controls

		ABO/Rh Blood Group								Total
		A+	A-	B+	B-	AB+	AB-	O+	O-	
Patient	N	784	112	299	55	140	27	539	88	2,044
Group	%	38.40	5.50	14.60	2.70	6.80	1.30	26.40	4.30	100.00
Control	N	1,121,702	154,330	434,143	59,626	200,972	28,582	894,210	129,318	3,022,883
Group	%	37.10	5.10	14.40	2.00	6.60	0.90	29.60	4.30	100.00

*P=0.016

Table 2. ABO/Rh Blood Group Distribution

	Lung cancer n (%)	Control n (%)	p	Odds Ratio
A	896 (43.8)	1,276,032 (42.2)	0.137	1.068
nonA	1,148 (56.2)	1,746,851 (57.8)		(95%CI. 0.979-1.166)
B	354 (17.3)	493,769 (16.3)	0.229	1.073
nonB	1,690 (82.7)	2,529,114 (83.7)		(95%CI, 0.957-1.203)
AB	167 (8.2)	229,554 (7.6)	0.325	1.080
nonAB	1,877 (91.8)	2,793,329 (92.4)		(95% CI, 0.924-1.269)
O	627 (30.7)	1,023,528 (33.9)	0.002	0.864
nonO	1,417 (69.3)	1,999,355 (66.1)		(95%CI, 0.787-0.950)
Rh+	1,762 (86.2)	2,651,027 (87.7)	0.040	0.876
Rh-	282 (13.8)	371,856 (12.3)		(95%CI, 0.773-0.994)

to 65 years old) –similar ancestry with patient's group- of Turkish Red Crescent between 2004 and 2011 were identified as a control group.

The relationship of ABO/Rh with clinical features such as age at diagnosis, histological subtype, and sex were evaluated. We compared the distributions of ABO/Rh among 2044 patients and 3,022,883 controls. Among patients, differences between each of aforementioned ABO/Rh groups with respect to various clinical features were explored, respectively.

This study was approved by the Institutional Review Board of Ankara University School of Medicine and conducted according to Helsinki Declaration and good clinical practice.

Statistical analysis was carried out using the computer program Statistical Package for the Social Sciences 11.5 for Windows (SPSS, Inc, Chicago, IL, USA). Frequency (percent) or median (minimum-maximum) were given as descriptive statistics. Chi-square test was used to determine differences in proportions. Mann-Whitney U test was used to compare two independent groups in terms of metric variables. P value of less than 0.05 was considered as statistically significant.

Results

Of these patients, the median age was 62 years (range: 17-90). Eighty four percent of the patients were male. In control group, 93% (2,818,330) was male and 7% (204,553) was female. There were no significant differences of blood groups regarding age and sex in control group. Overall distributions of ABO blood groups were significantly different between patients (43.8% A, 8.2% AB, 17.3% B, and 30.7% O) and controls (42.2% A, 7.6% AB, 16.3% B, and 33.9% O; p=0.023) (Table 1). In addition, there were significant differences between patients and controls with respect to Rh positive vs. Rh negative (p=0.040) and O vs. nonO (p=0.002). Whereas, the distributions of blood group regarding A vs. nonA, B vs. nonB, and AB vs. nonAB were not significantly different (Table 2). Likewise, among patients, there were no significant differences of blood groups with respect to sex, age, or histology.

Discussion

In present study, we showed that ABO blood type was associated with the lung cancer and having blood type other than O and having Rh-negative increase the risk of lung cancer. Overall, O blood group and Rh-positive were associated with a 14% and 13% risk reduction of lung cancer respectively.

There may be some explanations for this association. ABO blood group gene is mapped at the chromosome 9q34 and encodes blood group antigens related glycotransferases (Humphray et al., 2004). Blood group antigens are chemical components on the erythrocyte membrane but they are also expressed in a variety of epithelial cells including respiratory mucosal cells and mucus of bronchial gland mucous cells (Hakomori, 2001). In addition, various cancer cells express blood group antigens on their cell surface. In human lung cancer tissues, alterations of ABO antigen expression have been reported (Alvarez-Fernandez and Carretero-Albinana, 1991; Lee et al., 1991; Cerny et al., 1992; Miyake et al., 1992; Gwin et al., 1994; Rice et al., 1995; Graziano et al., 1997; Ulger et al., 2002; Sanchez-Mora et al., 2007; Leon-Atance et al., 2012).

Cancer and non-O blood group have associated with increased risk of thrombosis (Wu et al., 2008; Cohen et al., 2012). Furthermore, recent studies have reported an association between ABO blood group and the risk of various epithelial cancers. Non-O blood group increases risk of cancer including pancreatic, gastric, ovarian, kidney, colorectal and skin carcinomas (Wolpin et al., 2009; Edgren et al., 2010; Xie et al., 2010; Joh et al., 2012; Poole et al., 2012; Urun et al., 2012). Similarly, the thrombosis was associated with both increased risk of cancer and advanced disease and poor prognosis (Chew et al., 2006; 2007; Ahlbrecht et al., 2012). As well, venous thromboembolism (VTE) was associated with higher risk of death in patients with lung cancer (Chew et al., 2008). Individuals with nonO blood group have higher levels of von Willebrand factor (vWF) factor and VIII plasma levels. ABO blood group carbohydrates on VWF may influence susceptibility to proteolysis by ADAMTS13 (Bowen, 2003). In addition, genome wide association studies showed association between three single nucleotide polymorphisms (SNPs) on chromosome 9q34.2 and VTE (Heit et al., 2012). Likewise, an association between ABO blood group gene and SNP (rs505922) and

pancreatic cancer has been also identified (Amundadottir et al., 2009). For that reason, linkage disequilibrium between ABO blood group gene and cancer related gene might be another explanation.

Although, present study is a multicentric study and all blood group were serologically confirmed and diagnosis of lung cancer was pathologically confirmed there were some limitations. Because of retrospective nature of study, it is subjected to variety of bias including selection and referral bias. In addition, possible confounding factors that related with increased risk of lung cancer were not included.

In conclusion, in the study populations, ABO blood type was associated with increased risk of the lung cancer. Non-O blood group and Rh-negative features increased risk of lung cancer compared with blood group O and Rh-positivity. However, further prospective studies are necessary to define the mechanisms by which ABO blood type may influence the lung cancer risk.

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References

Ahlbrecht J, Dickmann B, Ay C, et al (2012). Tumor grade is associated with venous thromboembolism in patients with cancer: results from the vienna cancer and thrombosis study. *J Clin Oncol*, **30**, 3870-5.

Alvarez-Fernandez E, Carretero-Albinana L (1991). Expression of blood group antigens by normal bronchopulmonary tissues and common forms of pulmonary carcinomas. *Arch Pathol Lab Med*, **115**, 42-9.

Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al (2009). Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nat Genet*, **41**, 986-90.

Bowen DJ (2003). An influence of ABO blood group on the rate of proteolysis of von Willebrand factor by ADAMTS13. *J Thromb Haemost*, **1**, 33-40.

Cerny T, Fey MF, Oppliger R, et al (1992). Prevalence of the Rhesus-negative phenotype in Caucasian patients with small-cell lung cancer (SCLC). *Int J Cancer*, **52**, 504-6.

Chew HK, Davies AM, Wun T, et al (2008). The incidence of venous thromboembolism among patients with primary lung cancer. *J Thromb Haemost*, **6**, 601-8.

Chew HK, Wun T, Harvey D, Zhou H, White RH (2006). Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*, **166**, 458-64.

Chew HK, Wun T, Harvey DJ, Zhou H, White RH (2007). Incidence of venous thromboembolism and the impact on survival in breast cancer patients. *J Clin Oncol*, **25**, 70-6.

Cohen W, Castelli C, Alessi MC, et al (2012). ABO blood group and von Willebrand factor levels partially explained the incomplete penetrance of congenital thrombophilia. *Arterioscler Thromb Vasc Biol*, **32**, 2021-8.

Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ (2012). Lung cancer in never smokers--a review. *Eur J Cancer*, **48**, 1299-311.

Dela Cruz CS, Tanoue LT, Matthay RA (2011). Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med*, **32**, 605-44.

Edgren G, Hjalgrim H, Rostgaard K, et al (2010). Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. *Am J Epidemiol*, **172**, 1280-5.

Graziano SL, Tatum AH, Gonchoroff NJ, Newman NB, Kohman LJ (1997). Blood group antigen A and flow cytometric analysis in resected early-stage non-small cell lung cancer. *Clin Cancer Res*, **3**, 87-93.

Gwin JL, Klein-Szanto AJ, Zhang SY, et al (1994). Loss of blood group antigen A in non-small cell lung cancer. *Ann Surg Oncol*, **1**, 423-7.

Hakomori S (2001). Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anti-cancer vaccines. *Adv Exp Med Biol*, **491**, 369-402.

Heit JA, Armasu SM, Asmann YW, et al (2012). A genome-wide association study of venous thromboembolism identifies risk variants in chromosomes 1q24.2 and 9q. *J Thromb Haemost*, **10**, 1521-31.

Humphray SJ, Oliver K, Hunt AR, et al (2004). DNA sequence and analysis of human chromosome 9. *Nature*, **429**, 369-74.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Joh HK, Cho E, Choueiri TK (2012). ABO blood group and risk of renal cell cancer. *Cancer Epidemiol*, **36**, 528-32.

Lee JS, Ro JY, Sahin AA, et al (1991). Expression of blood-group antigen A--a favorable prognostic factor in non-small-cell lung cancer. *N Engl J Med*, **324**, 1084-90.

Leon-Atance P, Moreno-Mata N, Gonzalez-Aragoneses F, et al (2012). Prognostic influence of loss of blood group A antigen expression in pathologic stage I non-small-cell lung cancer. *Arch Bronconeumol*, **48**, 49-54.

Miyake M, Taki T, Hitomi S, Hakomori S (1992). Correlation of expression of H/Le(y)/Le(b) antigens with survival in patients with carcinoma of the lung. *N Engl J Med*, **327**, 14-8.

Poole EM, Gates MA, High BA, et al (2012). ABO blood group and risk of epithelial ovarian cancer within the ovarian cancer association consortium. *Cancer Causes Control*, **23**, 1805-10.

Rice TW, Tubbs RR, Hoeltge GA, et al (1995). Expression of blood group antigen A by stage I non-small cell lung carcinomas. *Ann Thorac Surg*, **59**, 568-72.

Sanchez-Mora N, Cebollero PM, Monroy V, Herranz AM, Alvarez-Fernandez E (2007). Expression of histo-blood group antigens in bronchial squamous metaplasia. *Eur Respir J*, **29**, 268-72.

Suadicani P, Hein HO, Gyntelberg F (2007). ABO phenotypes and inflammation-related predictors of lung cancer mortality: the Copenhagen Male Study - a 16-year follow-up. *Eur Respir J*, **30**, 13-20.

Ulger AF, Keklik T, Kumbasar OO, et al (2002). Prognostic significance of blood group antigen expression of tumor tissue in lung cancer patients. *Tumori*, **88**, 395-9.

Urun Y, Ozdemir NY, Utkan G, et al (2012). ABO and Rh blood groups and risk of colorectal adenocarcinoma. *Asian Pac J Cancer Prev*, **13**, 6097-100.

Wolpin BM, Chan AT, Hartge P, et al (2009). ABO blood group and the risk of pancreatic cancer. *J Natl Cancer Inst*, **101**, 424-31.

Wu O, Bayoumi N, Vickers MA, Clark P (2008). ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. *J Thromb Haemost*, **6**, 62-9.

Xie J, Qureshi AA, Li Y, Han J (2010). ABO blood group and incidence of skin cancer. *PLoS One*, **5**, 11972.