RESEARCH ARTICLE

ABO Blood Groups in Oral Cancer: A First Case-Control Study in a Defined Group of Iranian Patients

Hamed Mortazavi[1], Shima Hajian[2], Elnaz Fadavi[2], Siamak Sabour[3], Maryam Baharvand[1]*, Sedigheh Bakhtiari[1]

Abstract

The ABO blood group has been recently proposed to influence development of oral cancer. The aim of this study was to evaluate the association between the type of ABO blood group and oral cancer. In a case-control study, 104 patients with oral cancer were compared with 90 blood donors without cancer as controls. Data regarding the patient demographics, blood groups, Rh status, cancer characteristics and oral habits were also compared between two subgroups of squamous and non-squamous oral cancers. For statistical analysis, Chi-square test, t-student Test and Logistic Regression were used to analyze the relationship between ABO blood groups and oral cancer. The frequency of blood group B was significantly higher in oral cancer patients than controls (32% *vs* 13%) (p value=0.01), but Rh factor did not show significant difference between cases and controls. According to Logistic Regression, people with blood group B and those older than 50 had 3.5 and 19.4 times elevated risk of developing oral cancer, respectively. The frequency of squamous cell cancer was also significantly higher in men and people older than 50. On the other hand, females, people under 50, and those with blood group B were at 5.6, 2.9 and 4.3 times higher risk of developing non-squamous cell oral cancer,respectively. People with blood group B are at a greater risk of developing oral cancer, and female patients under 50 years of age with blood group B have the highest risk to develop non-squamous cell oral cancer.

Keywords: Blood group antigens - oral neoplasms - SCC - non-SCC - Iran

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Introduction

Cancer in its all forms accounts for about 12% of deaths throughout the world (Jaleel and Nagarajappa, 2012).Oral cancer has been estimated to be less than 3% of all cancers, but it is the eighth most common cancer in men and fifteenth most common one in women (Chi, 2009). It is found in 270 000 patients annually worldwide with the incidence of 1 in 20 000; this rises to 1 in 1100 in males of 75 years old and elder (Cawson and Odell, 2002; Amagasa, 2011). The occurrence of oral cancer is high in developing countries, such as Iran, so that two-thirds of the appearing cases are diagnosed in these countries (Fazeli et al., 2011). Oral cancer is the third most common malignancy after the cervix and stomach in developing countries (Fazeli et al., 2011). According to Amagasa, the number of individuals dying from pharyngeal and oral carcinoma is increasing approximately as threefold (Amagasa, 2011). Fazeli in an epidemiological study showed that mortality rate of the Iranian due to oral cancer increased dramatically from 0.09 per 100 000 in 1995 to 0.5 per 100 000 in 2002. However, Iran has a lower mortality rate because of oral cancer in comparison with other Asian countries. For example this rate is 7.2 per 100 000 in India (Fazeli et al., 2011). It is important to point out that the world mortality rate of oral cavity cancers has been reported as 2.9 per 100 000(Jemal et al., 2011).

Tobacco, alcohol and nutritional condition have been described as well-known factors associated with the increased risk of oral cancer. Other possible factors in the development of oral cancer such as viral infections and different expression of ABO blood group antigens are also being studied (Dabelsteen and Gao, 2005; Cerovic et al., 2008).

ABO antigens are not confined to red blood cells, but they are found on epithelial cells of various tissues such as mucosa and body fluids as well (Cerovic et al., 2008). Immunohistochemical evaluations of oral squamous cell carcinoma have reported loss of expression of A or B antigens in more than 80% of cases. The same findings were also shown in potentially malignant lesions with epithelial dysplasia (Gao et al., 2004; Dabelsteen and Gao, 2005). Gao demonstrated the different expression pattern of B antigens in normal, dysplastic and neoplastic tissues in blood group A/B as follows: the expression of B antigen was weak in normal epithelium, but was strongly

*[1]Oral Medicine Department, [2]General Dental Practice, [3]Clinical Epidemiology, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran *For correspondence: marbahar@gmail.com*

positive in dysplastic epithelial cells as well as in tumors. In addition, Gao reported that half of the leukoplakias developed in buccal mucosa had expression of an antigen (Gao et al., 2004).

Xie mentioned that the association between ABO blood group and the risk of cancer might vary among different races or ethnicities (Xie et al., 2010).

Therefore, the aim of this study was to evaluate the association between expression of ABO blood groups and epithelial and mesenchymal originated oral cancers. According to available data for us, this study was performed in a defined group of Iranian patients for the first time.

Materials and Methods

The present study was conducted at Department of Oncology, Taleghani hospital, Tehran, Iran, in year 2013. 104 patients comprising 69 (66%) males and 35 (34%) females who were histopathologically diagnosed of having oral cancer entered the study. Data regarding the patients' demographics, blood groups, Rh status, cancer characteristics (type, location, duration) and oral habits were obtained from their case history records available in the hospital.

Ninety people including 62 (69%) male, and 28 (31%) female, who had donated blood at this hospital or another centers for other oral problems except for oral cancer, as well as healthy population from blood donation centre were randomly selected and comprised as the controls. Such sampling method including patients without oral cancer from the same centre and another centre and also healthy population considered increasing generalizability of our results and minimizing probability of selection bias in case-control designs which usually occurs due to mistake in choosing controls. No matching considered since Logistic Regression can easily adjust for possible confounding factors.

In addition, cancer patients were divided into two subgroups: 1) patients with squamous cell originated oral cancer (oral squamous cell carcinoma (OSCC) and 2) patients with non-squamous originated oral cancers such as salivary gland tumors, mesenchymal tumors, and etc). Distribution of blood groups and Rh factor were also assessed in these two subgroups. For statistical analysis, Chi-square test, t-student Test and Logistic Regression were used to analyze the relationship between ABO blood groups and oral cancer.

Results

Demographic data of all participants and the distribution of blood groups among case and controls were shown in Table 1.

According to this table, frequency of blood group B in patients with oral cancer was significantly higher than control group (p=0.01). However, there was no significant difference between case and control group in terms of Rh factor (RhD+ and RhD-) (p=0.5).

Demographic data and distribution of blood groups of cancer patients according to cancer type was shown in Table 2. According to this table, the incidence of squamous cell originated cancer was significantly higher in men and people older than 50 years of age, whereas non-squamous cell originated cancers were mostly frequent in women and people younger than 50 (p=0.00, p=0.00). Meanwhile, there were no significant differences in the frequency of blood groups and Rh factor (RhD+ and RhD-) between patients with squamous and non-squamous cell originated cancers (p= 0.53, p=0.91).

In addition, Logistic Regression demonstrated that people with blood group B (compared to blood group O) and those older than 50 years of age (compared to younger patients) had 3.5 and 19.4 times higher risk of developing oral cancer, respectively (Table 3).

On the other hand, Logistic Regression showed that

Table 1. Demographic Data and Distribution of Blood Groups among Case and Controls

Variable		Case N (%)	Control N (%)	Total
Sex*	Male	69(66%)	62(69%)	131(68%)
	Female	35(34%)	28(31%)	63(32%)
	Total	104(100%)	90(100%)	194(100%)
Age**	<50Yrs	26(25%)	75(83%)	101(52%)
	>50Yrs	78(75%)	15(17%)	93(48%)
Blood group***	O	38(36%)	39(43%)	77(40%)
	A	25(24%)	24(27%)	49(49%)
	B	33(32%)	12(13%)	45(23%)
	AB	8(8%)	15(17%)	23(12%)
Rh factor****	Rh+	86(83%)	77(86%)	163(84%)
	Rh-	18(17%)	13(14%)	31(16%)

*p value=0.70(Chi-square test),**p value<0.00(Chi-square test),***p value= 0.01(Chi-square test), ****p value=0.58(Chi-square test)

Table 2. Demographic Data and Distribution of Blood Groups according to Cancer Type

Variable		Squamous Cell originated	Non-Squamous Cell originated	Total
Sex*	Male	56(74%)	13(43%)	69(66%)
	Female	18(24%)	17(57%)	35(34%)
	Total	74(100%)	30(100%)	104(100%)
Age**	<50Yrs	12(14%)	14(47%)	26(25%)
	>50Yrs	62(84%)	16(53%)	78(70%)
Blood group***	O	30(41%)	8(27%)	38(36%)
	A	17(23%)	8(27%)	25(24%)
	B	21(28%)	12(40%)	33(32%)
	AB	6(8%)	2(7%)	8(8%)
Rh factor****	Rh+	61(82%)	25(83%)	86(83%)
	Rh-	13(18%)	5(17%)	18(17%)
	Total	74(100%)	30(100%)	104(100%)

*p value=0.00 (Chi-square test), **p value=0.00 (Chi-square test),***p value= 0.53(Chi-square test), ****p value=0.91 (Chi-square test)

Table 3. Risk of Developing Oral Cancer in Terms of Age, Sex,Blood Group, and Rh Status

Variables	df*	p value	OR**	95% CI***	
				Lower	Upper
Age (≥50yr)	1	0	19.4	8.83	42.8
Sex (Male)	1	0.08	0.5	0.23	1.1
ABO (O)	3	0.01			
ABO (A)	1	0.74	0.85	0.34	2.15
ABO (B)	1	0.01	3.5	1.3	9.27
ABO (AB)	1	0.29	0.51	0.14	1.79
Rh +	1	0.67	0.8	0.29	2.19
Constant	1	0.02	0.42		

*df: degree of freedom; ** OR: odds ratio; ***CI: confidence interval

Table 4. Risk of Developing Squamous and Non-Squamous Originated Oral Cancer in Terms of Age, Sex, Blood Group, and Rh Status

Variables	df*	p value	OR**	95% CI ***	
				Lower	Upper
Age (<50yr)	1	0.04	2.94	1.03	8.36
Sex(Female)	1	0	5.61	1.74	18
ABO(O)	3	0.22			
ABO(A)	1	0.12	2.97	0.74	11.8
ABO(B)	1	0.03	4.38	1.07	17.9
ABO(AB)	1	0.41	2.25	0.31	15.9
Rh (+)	1	0.37	0.51	0.11	2.24
Constant	1	0	0.07		

*df: degree of freedom;** OR: odds ratio; ***CI: confidence interval

females (compared to males), people under 50 (compared to older people) and people with blood group B (compared to blood group O) had 5.62, 2.95 and 4.38 times higher risk of developing non-squamous cell-originated oral cancers, respectively (Table 4).

Discussion

Lipid or protein-bound carbohydrates (glycolipids or glycoproteins) are found on cell membrane, which may undergo some changes during cell maturation or malignant transformation as shown by some previous studies (Fukuda, 2002; Hakomori and Handa, 2002; Hakomori, 2003; Gao, et al., 2004; Dabelsteen and Gao, 2005). Most of the time, the outer part of such glycoconjugates includes carbohydrates like ABO and Lewis blood group antigens (Dabelsteen and Gao, 2005). A high incidence of various carcinomas are found in patients having A/B blood groups, which may be due to higher affinity of these antigens to some micro organisms known to develop cancer (Dabelsteen and Gao, 2005). Several reasonable mechanisms have been proposed to explain the relationship between ABO blood groups and risk of cancer such as inflammation, immunocompetency to detect malignant cells, intercellular adhesion and membrane signaling (Xie, et al., 2010). Down regulation of glycosyl transferase that is involved in the biosynthesis of A and B antigens, and linkage disequilibrium between ABO genes with other genes may help promote carcinogenesis (Wolpin et al., 2009; Xie, et al., 2010; Jaleel and Nagarajappa, 2012).

ABO antigens can also be present on key receptors such as EGF receptors, integrins , cadherins and CD-44, which control cell proliferation, adhesion and motility. As the expression patterns of these receptors vary in normal and cancerous cells, the role of ABO antigens in tumerogenesis may be different as well(Biondi, et al., 2008).

In this study, among oral cancer cases, male: female ratio was 2:1,and most of the patients (75%) were older than 50 years of age. These findings were in agreement with Jaleel (Jaleel and Nagarajappa, 2012). Cawson also suggested that oral cancer is an age-related disease, and 98% of patients are over the age of 40 (Cawson and Odell, 2002). However, in recent decades an upward trend has been observed in the number of oral cancer cases among women and younger age groups (Fazeli, et al., 2011).

On the basis of the present study, blood group B was significantly more frequent in oral cancer patients than control group. Furthermore, Logistic Regression demonstrated that people with blood group B and those older than 50 years of age had 3.5 and 19.4 times risk of developing oral cancer, respectively.

In accordance to our findings, Akhtar showed a high incidence of blood group B (37.5%), in patients with oral cancer, which was followed by A (35%), O (20%) and AB (7.5%) blood groups (Akhtar, et al., 2011).

Sharma and colleagues also demonstrated that in cancer of the buccal mucosa blood group B had the highest frequency (34.1%), followed by A (30.4%), O (28.0%), and AB (7.3%)(Sharma, et al., 2007). Jovanovic-Cupic et al. (2008) evaluated the relationship between ABO blood groups and malignant tumors of the digestive tract in Bosnia and Herzegovina, and found a significantly higher frequency of blood group B in cancer patients.

Jaleel in an other study from India showed that people with blood group A had 1.4 times higher risk of developing oral cancer followed by B blood group (1.1 times), AB (0.9 times) and O (0.6 times) (Jaleel and Nagarajappa, 2012). Other studies, which were done in India, have demonstrated individuals with blood group A have predisposition for oral cancer (Tyagi, et al., 1965; Mital and Gupta, 1969; Nayak, 1971; Baruah and Gogoi, 1977). These differences in findings may be related to diversity in sample size, study design and races of participants (Xie et al., 2010).

Yu, Guleria, and Xie noted that association between ABO blood groups and the risk of cancer may vary among different geographic localizations and races or ethnicities (Yu et al., 2000; Guleria et al., 2005; Xie et al., 2010).

Unfortunately, there is lack of information about association between ABO blood groups and oral cancer in Iranian population to compare with our study.

In addition, Xie in a study from US, evaluated the relationship between ABO blood groups and skin cancers, and showed that the risk of developing SCC was significantly lower for patients with blood group A. The same results were found in patients with BCC, but they did not observe a statistically significant decreased risk of developing melanoma in participants with non-O blood groups (Xie et al., 2010).

Our study also showed that blood groups O and B were more frequent in squamous and non-squamous cell originated oral cancers, respectively. But there were no significant differences between these two types of oral cancer in terms of ABO blood groups and Rh factor.

According to our results the incidence of squamous cell originated cancer was significantly higher in men and people older than 50 years of age whereas, non-squamous cell originated cancers were more frequent in women and people younger than 50.

Logistic Regression showed that females, people younger than 50 years of age and people with blood group B had 5.6, 2.9 and 4.3 times higher risk of developing non-squamous cell originated oral cancer, respectively.

According to our results there was no relationship between Rh factor and developing of oral cancer. In agreement with us, review of literature showed that

most authors did not find any relationship between Rh factor and human carcinogenesis (Pinkston and Cole, 1996; De Manzoni et al., 2001). However, Jovanovic-Cupic concluded that patients with RhD-exhibited a significantly higher proportion of digestive tract cancer (Jovanovic-Cupic et al., 2008). Also Bryne suggested that the prognosis of five-year survival in RhD+ cancer patients is considerably better than those with RhD-(Bryne et al., 1991).

The effect of Rh system in pathological processes may be related to the physiological role of very different and complex proteins of Rh system in the transport of toxic biological gases such as ammonia or carbon dioxide to detoxifying organs, e.g. the liver or kidney. Furthermore, association between RhD-and cancers might be related to linkage disequilibrium.

The Rh gene locates on the short arm of chromosome 1 where some oncogenes are also located, but linkage analysis for these genes is still unclear (Jovanovic-Cupic et al., 2008).

Pourfathollah showed that the frequency of blood group O and B have increased 1.3% during twenty years from 1982 to 2001 among Iranian patients, whereas the frequency of blood group A has decreased by 2%. In some provinces such as Isfahan, Ilam, Fars, Kordistan, Khuzistan, Hormozgan and Yazd, the blood group frequencies have shown more alterations (Pourfathollah, et al., 2004).

Health care providers involved in cancer screening and preventive programs should take this finding into consideration in addition to our results.

In conclusion, people with blood group B are at a greater risk to develop oral cancer, and female patients under 50 years of age with blood group B have the highest risk to develop non-squamous cell originated oral cancers.

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