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**ABO blood groups are risk factors for Oral squamous cell carcinoma**

**Abstract**

**Introduction:** In the last few years, blood groups were proposed as risk factors for the development of cancer, cardiovascular disease, neurological problems and surprisingly even infectious diseases.

**Objectives:** The goal of this research was to understand the relationship between blood groups and oral cancer.

**Methods:** This study was conducted to evaluate the incidence of blood groups among 160(males=98; females= 62) oral cancer patients as compared with 200 healthy controls (males =100; females=100). For statistical analysis ‘Chi-square test’ and ‘Odds ratio’ were used to determine whether any particular blood group is a risk factor for oral cancer.

**Results:** It was found that individuals with blood group A had 1.65 times increased risk of developing oral cancer (odds ratio= 1.65; P<0.05; significant) as compared with other blood groups. The relative risk for blood group ‘B’ was 1.28 and for blood group ‘O’, it was 0.55. Individuals with blood Group ‘O’ were associated with lower odds of developing oral cancer (Odds ratio = 0.55; P< 0.01, Highly Significant).

**Conclusion:** The results show that the incidence of oral cancer is significantly higher among people with blood group ‘A’ and significantly lower among people with blood group ‘O’.

**Keywords:** ABO antigens, blood groups, oral cancer risk, linkage dis-equilibrium.

**Introduction:** Oral cancer, 90 percent of which are oral squamous cell carcinomas (OSCC), are common malignancies that are associated with a very high mortality rate [1]. Its incidence has dramatically increased (0.09 per 100,000 in 1995 to 0.59 per 100,000 in 2002) during the last few years according to the studies of Fazeli et al [2]. Fazeli’s study was conducted on Iranian population, and in countries like India the burden is still higher. In India, more than 100000 cases are registered every year and Bhopal has the highest incidence of oral cancer in the world [3].The most common risk factors for oral cancer include tobacco usage either in chewable form (gutka) or in smoke form, alcoholism, diet deficient in antioxidants, nutritional status, human-papilloma virus (HPV-16) and genetic factors (P53 mutations, single nucleotide polymorphism A/G870 in the CCND1gene) [4, 5, 6]. Blood groups and Rh factor are less recognized risk factors for oral cancer.

The first inquiry into the distribution of blood groups in patients with malignancy was made by W.Alexander in 1921 [7]. In his study he determined the blood groups of 50 patients who had malignant disease (carcinoma, sarcoma, rodent ulcer, leukemia) and the incidence was compared with 125 patients with other maladies and 50 normal controls. After 33 years, Aird et al reported a similar association between blood groups and cancer. They observed that blood group ‘A’ was associated with an increased risk of stomach cancer [8]. Since then, blood groups were proposed as risk factors for skin cancer, pancreatic cancer, gastric cancer, ovarian cancer, lung cancer, acute lymphoblastic leukemia, cardiovascular disease, venous thromboembolism, pre-eclampsia and several others, but, only a few studies have examined the link between blood groups and oral cancer [9, 10, 11, 12, 13].

Oral cancer progression is associated with altered glycosylation of several cell surface proteins and lipids [14]. Blood group antigens (A and B) are carbohydrate structures that are formed by the addition of monosaccharides to the carbohydrate side chains of glycolipids and glycoproteins [15]. They are present on the cell surface of red blood cells, sensory neurons, platelets, endothelial cells, oral epithelial cells (chiefly expressed by the non-keratinized epithelium) and other cells [16, 17]. The ‘H antigen’ serves as a precursor for both A and B antigens [18]. The alleles at the ABO locus (9q34) encodes enzymes (alpha -N-Acetyl –D-Galactosaminyl transferase ; alpha-D-Galactosyl transferase) which catalyzes the addition of N-Acetyl –D-Galactosamine or D-Galactose to H antigen to form the A and B antigens respectively [ 19, 20 ] (Figure 1). Based on the presence of these blood group antigens, individuals are classified into four groups - A, B, AB or O.

**Methods:** This study was Conducted in the Department of Oral medicine and Radiology, MNR Dental College, Telangana state, over a period of 2 years (from 2012 June to 2014 august) after obtaining clearance from the institutional ethical committee. A total of 160 patients comprising 98 males and 62 females who were histopathologically diagnosed with oral squamous cell carcinoma were included in the study. The control group consisted of 200 people (100 males and 100 females) who had donated blood at the medical hospital of our institution, during the same time. For cancer patients, data regarding habits, cancer characteristics (location, duration) and blood groups were obtained from the case sheets. For statistical analysis, chi-square test and odds ratio were used to assess the association between ABO blood groups and oral cancer. The significance level was fixed at ≤0.05.

**Results:** In this study a higher incidence (Statistically significant; p<0.01) was noted with regard to the incidence of oral cancer among males. The male to female ratio was approximately 3:2. ‘Table 1’ shows the incidence of ‘ABO’ blood groups among the males and females of 160 oral cancer patients. There were 98 males and 62 females in this study. Out of 98 males, 34(37%) had blood group ‘A’, 24 (26%) had ‘B’, 33(36%) had ‘O’ and 1(1%) had ‘AB’. Out of 62 females, 17(25%) had blood group A, 24(35%) had ‘B’, 24(35%) had ‘O’ and 3(5%) had ‘AB’. The frequency of blood groups among male cancer cases was A>O>B>AB and among females cases it was O>B>A>AB.

‘Table 2 and Graph 1’ show the distribution of different blood groups among the cancer and control group. In this study there were 160 cancer cases and 200 controls. Among the 200controls, 44 (22%) had blood group A, 50(25%) had B, 100(50%) had O and 6(3%) had AB (Graph 2). The frequency of blood groups among control group was O>B>A>AB. Among the 160 cancer cases, 51(32%) had blood group A, 48(30%) had B, 57 (36%) had O and 4(2%) had AB (Graph 3). The frequency of blood groups among the cancer group was O> A>B>AB. The incidence of blood group A was statistically significant (P=0.04; P<0.05) among the cancer group and the relative risk was 1.65(odds ratio=1.65) as compared to other blood groups. The incidence of blood group B was higher (odds ratio=1.25) among the oral cancer group as compared to controls, but it is not statistically significant (P= 0.3). The incidence of blood group AB is relatively less (odds ratio= 0.83) among oral cancer subjects as compared to healthy controls, but it is not statistically significant (P= 0.7). There was a marked decrease in the incidence of blood group O among oral cancer patients as compared to healthy controls. Individuals with blood group ‘O’ were associated with lower odds (Odds ratio = 0.55) of developing oral cancer (P< 0.01; Highly Significant). A Majority of cases occurred on the buccal mucosa (65%) followed by tongue (23%), alveolus (10%), floor of mouth (2%) ( Graph 4) .

**Discussion:** This study demonstrates the association between blood groups and oral cancer. Molecular genetic studies suggested that the tumor suppressor genes located on chromosome 9(9p21-23)are involved in the pathogenesis of oral cancer (21, 22, 23). Studies on the human ABO gene have indicated that the events leading to a loss of transferase activity are related to loss of Heterozygosity (LOH) involving 9p34, which is the locus for the ABO gene and in other cases to a hypermethylation of the ABO gene promoter [24, 25, 26]. There may be linkage dis-equilibrium (LD) between the ABO gene and the tumor suppressor genes (Figure 1). Linkage disequilibrium is the association of alleles at two or more loci that descended from single, ancestral chromosomes. It denotes the correlation between the neighboring alleles. Previously, LD was thought to extend only a few kilobases (kb), but recent data suggest that LD may sometimes extend much further, greater than 100 kb [27].

The A and B antigens are present on receptors (integrins, cadherins etc) that control key cellular process such as cell adhesion, proliferation and motility. Loss of A/B antigens was evident in 80% of oral cancer cases and 50% of leukoplakia cases (loss of A/B antigens in dysplastic leukoplakia > non-dysplastic leukoplakia) [28]. Dabelsteen, Pindborg and Hokomori concluded that in carcinomas, blood group A antigen decreases in amount or completely disappears [14, 19, 25]. A relative down-regulation of glycosyl-transferase that is involved in the biosynthesis of A and B antigens is a possible explanation for the altered antigen pattern. [14]

As discussed earlier, In people belonging to A and B blood groups, the precursor H is converted to A or B where as in individuals with blood group O, it remains in its original form (Figure 1). Individuals with blood group O have the highest amount of H antigen, and it is believed to have a protective role against oral cancer. In the present study, there was a lower incidence of oral cancer among individuals with blood group O, which can be attributed to H antigen. ‘Antigen H’ certainly confers a protective role against oral cancer. This finding is consistent with the studies of Jaleel B et al [29].

**Bombay blood group can serve as a model:** A special situation arises, when there is a homozygous deficiency of ‘FUT 1 gene’ [30]. In such cases (Bombay phenotype) the ‘H precursor’ is completely absent and hence it cannot be modified into A and B antigens [31]. As a result, individuals with Bombay blood group with a history of tobacco usage may be highly susceptible for oral cancer. But as of now, no studies are available. The Bombay blood group can actually serve as a model to understand the relationship between ‘H antigen’ and oral cancer, and future studies should explore this area. However, great difficulty will be encountered by researchers owing to the very low incidence of Bombay blood group. The incidence in India is 1in 10000 and in Europe it is 1 in 1000000 [32].

The present study concluded that patients with blood group A have an increased suseptibility to oral cancer. This finding is in agreement with the studies conducted by Raghavan et al, Tyagi et al, Mittal et al, Nayak and Baruah et al [33, 34, 35, 36, 37]. According to a recent study which compared the incidence of different blood groups among controls and patients with leukoplakia and oral submucous fibrosis, it was shown that 24 % of gutka chewers who had higher grades of dysplasia belonged to Blood group A [38].

In the present study, the male to female ratio among the oral cancer cases was 3:2. This increase in the number of cases among males is due to their heavier indulgence in tobacco related habits [2]. Buccal mucosa was the most common site in the study population accounting to 65%. According to a review by Saman Warnakulasuriya, 40-50% of oral cancer cases in asia were observed on the buccal mucosa [2]. This is due to the wide use of tobacco products in chewable form and also due to the placement of quid in the buccal vestibule. The next frequent site was tongue (23%) followed by the alveolus (10%).

**Conclusion:** This study identified a significant association between ABO blood groups and oral cancer which indicates that they share a genetic link. In the present study, the incidence of oral cancer was significantly higher among individuals with blood group ‘A’ and significantly lower among individuals with blood group ‘O’. Antigen ‘H’ seems to have a protective effect against the development of oral cancer. ‘Blood grouping test’ can be used as a screening tool in predicting the susceptibility of oral cancer and it might also help in assessing the risk of malignant transformation of oral pre-cancer. As blood group A confers a higher risk, candidates with this blood group should be carefully counseled regarding the withdrawal of habits. Though the exact mechanism behind the association between blood groups and oral cancer is poorly understood, it can be attributed to linkage disequilibrium between the two genetic loci. Further studies are needed to understand this relationship at a genetic level.

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**Figure 1 :** Blood groups and oral cancer are related at a genetic level.

**Graph 1:** Relative distribution of ABO blood groups among cancer and control group

**Graph 2:** Distribution of ABO blood groups among control group

Graph 3: Distribution of ABO blood groups among cancer group

Graph 4: Distribution of oral cancer cases based on the site of involvement.

**Tables 1:**

|  |
| --- |
| **ABO blood groups among cancer cases(n=160)** |
| **Male cancer cases(n=98)** | **Female cancer cases(n=62)** |
| 34(37%) blood group A | 17(25%) blood group A |
| 24(26%) blood group B | 24(35%)blood group B |
| 1(1%) blood group AB | 3(5%)blood group AB |
| 33(36%) blood group O | 24(35%)blood group O |

Legend to Table 1: Gender-wise distribution of ‘ABO’ blood groups among 160 oral cancer patients

**Table 2:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Blood group** | **Oral cancer cases (n=160)** | **Controls****(n=200)** | **Odds Ratio** | **Confidence Interval** | **P-Value** |
| **Lower****limit** | **Upper limit** |
| A | 51(32%) | 44(22%) | 1.65 | 1.03 | 2.65 | 0.04(S) |
| B | 48 (30%) | 50(25%) | 1.28 | 0.80 | 2.04 | 0.3 |
| AB | 4(2%) | 6 (3%) | 0.83 | 0.23 | 3.02 | 0.7 |
| O | 57 (36%) | 100(50%) | 0.55 | 0.36 | 0.84 | 0.006(HS) |

 ‘S’ stands for significant

 ‘HS’ stand for highly significant

 Legend to Table 2: The strength of association between blood groups and oral cancer