

*Review Article***Is Blood group an important factor in oral cancer? – A Review**

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**Abstract:** Oral cancer has multifactorial aetiology and is significantly associated with various risk factors of the individual's lifestyle, particularly, chronic use of tobacco, spicy food, alcohol and smoking. Many studies have indicated that genetic factors also have an influence on the aetiology of cancer. Biochemical and molecular genetic studies have contributed to our molecular knowledge of blood group-associated molecules in the past few years. Among the 30 blood group systems presently identified, almost all have a molecular basis and present investigations are oriented towards the analysis of genetic polymorphisms, tissue-specific expression and structure-function relationships. Various studies have indicated susceptibility of different blood groups for specific head and neck cancers. Existing researches link these factors with the development of cancer, but the results are different and still only hypothesis which have to be proven. It may be conceded that the presence of the particular blood group or genes or antigen has somehow increased the susceptibility to the disease. The applied method of search or the search strategies were books, printed articles, google, and pubmed database. The available review materials between the years 1965 to 2015, concerned only with oral potentially malignant disorders and oral cancer were referred. This comprehensive review on role of blood groups as an aetiology in oral cancer is attempted to highlight the importance of susceptibility of different blood groups for head and neck cancers.

**Key words:** Oral cancer; Blood group; Genetics; Aetiology; Potentially malignant disorders.

## INTRODUCTION

The term "oral cancer" includes a diverse group of tumors arising from the oral cavity. The vast majority of malignant neoplasms in the mouth are squamous cell carcinomas. Oral cancer incidence and mortality rates vary widely across the world. It is important to diagnose oral cancer in its early stages, since the management of small and localized tumors involves less morbidity and mortality than more advanced-stage disease, where treatment must be more aggressive. Indeed, the stage in which the disease is diagnosed is directly correlated to long-term survival.<sup>1,2,3</sup> Human genetics is much more than the study of mere hereditary diseases. It has emerged as a basic biological science for understanding the endogenous factors in health and disease and the complex interaction between nature and nurture. Blood groups A, B and O were discovered by Karl Landsteiner in 1900 and the 4th group AB was later described by his pupils.<sup>3</sup> Alexander in 1921 was first to describe the possibility of association between ABO blood groups and malignancy.<sup>4</sup> The ABO blood type system comprises 4 blood groups: O, A, B, and AB.

Blood group antigens, which are the major allo antigens in humans, are present on the surface of red blood cells and various epithelial cells. As the majority of human cancers are derived from epithelial cells, changes in blood group antigens are an important aspect of human tumor.<sup>5</sup> Tyagi et al (1965) showed, in Indian population, that patients with blood group A have predisposition for oral cancer.<sup>6</sup> Recently, Jaleel and Nagarajappa (2012) showed similar results in their study with increased risk of oral cancer associated with blood group A.<sup>7</sup> Apart from cancers ABO blood groups have also been associated with disease entities, such as pulmonary tuberculosis, leprosy, syphilis, malaria, coronary artery disease, diabetes mellitus.<sup>8</sup> The ABO blood group distribution varies in different geographical, ethnic and socio-economic groups.<sup>9</sup>

## DISCUSSION

**Relationship between ABO blood group and potentially malignant disorders**

In India prevalence of leukoplakia varies from 0.2 to 5.2%, erythroplakia 0.02% and OSMF

varies from 0.16 to 3.2.<sup>10</sup> The term 'Oral potentially malignant disorders' (OPMD) is recommended by WHO in the year 2005.<sup>11</sup> It includes both oral premalignant lesions and conditions. The prevalence of oral premalignant lesions and oral cancer is very high in India. The oral premalignant lesion is an intermediate clinical state with increased risk of cancer, which can be recognized and treated with a much better prognosis compared to the full blown malignancy. Some of the major oral potentially malignant disorders are leukoplakia, erythroplakia and oral submucous fibrosis.<sup>12,13</sup> In a study by Chordia et al (2015), demonstrated that people with blood group A are 3.98 times at a greater risk to develop OSMF where as with respect to oral cancer risk in blood group A was found to be 27%, followed by those with blood group AB, B and O.<sup>3</sup> In a similar study done by Vaish et al (1979) blood group A was associated with leukoplakia and oral submucous fibrosis.<sup>14</sup> Kumar et al. (2014) observed the association of ABO blood grouping with OLP in 52 cases and reported that blood group A had 1.28 times higher risk of developing OLP.<sup>4</sup>

Certain blood group is considered more prone to develop premalignancy and subsequently convert to malignancy. This is explained by the fact that blood group antigen in addition to being present on red blood cell membranes are also found on epithelial cells of various other tissues, including the oral mucosa. The relative down-regulation of glycosyl transferase that is involved in biosynthesis of A and B antigen is seen in association with tumor development.<sup>15</sup> H antigen is precursor for the formation of A and B antigen and is present in all the individuals irrespective of blood group types. H antigen is converted into A and B antigens in people belonging to A and B blood group. Where as in O blood group individuals H antigen remains in its original form. People with O blood group have highest amount of H antigen which affords protection, hence least susceptible to develop oral cancer.<sup>16</sup>

The OPMD and oral cancer are considered to be the disease of older age. Majority of males

have been reported with OSMF followed by leukoplakia, while in females leukoplakia was the most common followed by OSMF. This dramatic increase in oral submucous fibrosis has been attributed to various etiological factors of which gutka and paan masala chewing are predominantly very common.<sup>17</sup> Thus identifying these lesions at an early stage and rendering treatment is very important for decreasing the mortality rate due to their malignant transformation.<sup>12</sup> A study by Dabelsten & Gao (2004) have demonstrated that there exists a relationship between ABO blood groups and OLP. People having blood group A were found to have a greater tendency to develop OLP, which is further a premalignant disorder. This can be explained by the fact that blood group antigens, in addition to being present on red blood cell membranes, are also found on epithelial cells of various other tissues, including the oral mucosa. The relative down regulation of glycosyltransferase, which is involved in the biosynthesis of A and B antigens, is seen in association with tumor development.<sup>15</sup> Partial or complete deletion of epithelial blood group antigens due to aberrations in their synthesis brings about changes in their cell surface. It has been indicated that the altered antigen pattern on the cell surface is a tumor-related change.<sup>18</sup>

#### **Relationship between ABO blood group and oral cancer**

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. Oral cancer is the third most common malignancy after the cervix and stomach in developing countries. According to Amagasa (2011), the number of individuals dying from pharyngeal and oral carcinoma is increasing approximately as threefold.<sup>19-23</sup>

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.<sup>16</sup>

Dabelsten & Pindborg (1973) reported a higher incidence of oral cancer in blood group A and B individuals as compared to the others.<sup>18</sup> Raghavan et al (1986), studied the incidence of ABO blood group in oral cancer in south Kanara district, India and concluded that there is increased susceptibility of blood group A to oral cancer.<sup>19</sup>

More than 20 genetically determined blood group systems are known today but ABO blood groups are sensitive than other blood grouping system in detecting antigen responsible for cancers as ABO blood group genes are mapped at 9q34.2 region in which genetic alteration is common in many cancers. Thus, blood group antigen expression may be affected by genetic change of tumor, the loss or presence of blood group antigens can increase cellular motility or facilitate the interaction between tumor cells and endothelial cells of distant organs.<sup>24-25</sup>

In many cancers, the deficiency of A or B epitope has been reported, which is associated with the accumulation of their precursor, which causes enhanced malignancy, although the molecular genetics mechanism leading to such phenotypic changes is not known. The expression of certain blood group carbohydrate antigens on the surface of cancer cells thus can be regarded as an end product of tumor progression that can be used as useful prognostic and diagnostic markers.<sup>26</sup> Lipid or protein bound glycoprotein are found on cell membrane, which may undergo some changes during cell maturation or malignant transformation as shown by some previous studies.<sup>27</sup> Most of the time, the outer part of such glycoconjugates includes carbohydrates like ABO blood group and Lewis antigens. A high incidence of various carcinomas are found in patients having A/B and these antigens have higher affinity to some micro organisms known to develop cancer.<sup>16</sup>

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. Down regulation of glycosyltransferase that is involved in the biosynthesis of A and B antigens may help promote carcinogenesis.<sup>28-29</sup> 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 tumor genesis may be different as well.<sup>30</sup>

Motazavi et al (2014), evaluated the association between the type of ABO blood group and oral cancer in 104 patients with oral cancer and 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. They concluded that 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 highest risk to develop non-squamous cell oral cancer.<sup>31</sup>

In another study done by Singh et al (2014), the authors observed that Blood group A had 1.84 times higher risk for Oral cancer. Blood group A had increased risk for esophageal and salivary gland cancer and blood group B for laryngeal cancers. They concluded that there is an inherited element in the susceptibility and risk of various head and neck cancers and that racial and ethnic distribution of blood group is important factor in predicting cancer risk.<sup>32</sup>

Gao et al (2004), conducted a study with an aim to investigate genotypic alterations in the ABO locus in oral potentially malignant lesions and carcinomas. Both tumour and normal cells were collected from paraffin-embedded tissue by laser microdissection. DNA was extracted and analysed by PCR coupled with restricted digestion analysis in order to establish the ABO genotype. Total and patchy loss of A/B antigen expression was found in 24/32 carcinomas, 6/7 leukoplakias with severe dysplasia, 12/17 leukoplakias with

mild and moderate dysplasia, and 6/17 leukoplakias without dysplasia. Specific A/B allele loss was found in 8/24 cases with carcinoma and 3/24 cases with mild and moderate dysplasia by genotyping analysis. The authors concluded that Loss of A/B antigen expression in tissues which had intact ABO alleles was, however, found and may be explained by other genetic and epigenetic changes.<sup>33</sup>

Campi et al (2007), investigated the secretor status of patients with oral pre-cancerous and cancerous lesions and ABH antigens of patients and suggested the use of secretory method to monitor probable pre neoplastic lesions in risk population, especially in those with no secretor status.<sup>34</sup> Cerovi et al (2008), investigated that though existing laboratory and clinic researches do not show the correlation between ABO blood group antigens and the development of oral carcinoma, this is not clinically confirmed. A few existing clinical researches have been conducted on a small number of examinees and results vary a lot.<sup>35</sup>

Jaleel & Nagarajappa (2012), evaluated to know whether ABO blood groups are associated with an increased risk for oral cancer. The results showed that people with blood group A had 1.46 times higher risk of developing oral cancer compared to people of other blood groups.<sup>7</sup> Rai et al (2015), assessed the relationship between ABO blood group and secretor status of the 45 patients with OPMD. The Wiener agglutination test was performed to analyze the secretor status. The results demonstrated a statistically significant relation between OPMDs and secretor status. But there was no statistically significant relationship between ABO blood groups and OPMDs. The conclusion of their study stated that, the inability to secrete blood group antigens in the saliva of patients with OPMDs could be regarded as a host risk factor and the results could not propose a relationship between ABO blood group and OPMDs.<sup>36</sup>

Akhtar et al (2010), described incidence of ABO blood group in cancers, so as to assess

the utility of ABO blood group as a preclinical marker. Samples of 2640 histologically proven head and neck cancer patients were collected from the Blood Bank (Aligarh) reported from 2000 to 2007. When all head and neck cancers were taken together, the highest frequency of blood group was B (40.5%), followed by A (34.2%), O (16.0%) and AB (9.3%) was seen. The frequency of A group was significantly higher and O group was significantly lower in cancer patients as compared to controls. A high incidence of blood group B (37.5%) followed by A (35%) was seen in oral cancers. They concluded that racial and ethnic distribution of blood groups is an important factor for predicting cancer risk and the identification of genetic and environmental factors among racial and ethnic groups should offer some insights into an observed epidemiological data and opportunities to better understand the control and development of cancer.<sup>37</sup>

Clinical examination and histopathological studies of biopsied material are the classical and the most accepted diagnostic methods used for precancerous and cancerous oral lesions. While conventional oral examination may be useful in the discovery of some oral lesions, it does not identify all potentially premalignant and/or malignant lesions.<sup>1</sup>

Various studies indicate that there is susceptibility of different blood groups for specific/ various head and neck cancers which creates a need to spread responsiveness among the susceptible groups who should be trained for self examination and should be encouraged for early referral of cancer screening clinics if they observe any symptoms.<sup>32</sup>

Specific area Volunteers or health professionals and clinicians can be a support, as a part of various programs in villages or other areas like tobacco cessation programs who can help in bringing awareness about the cancer and its various preventive methods to people in the neighboring areas.<sup>32</sup>

**CONCLUSION:** It appears that different blood groups have been associated with

different manifestations of the disease. From the above association of blood groups and various cancers, it follows that there is an inherited element in the susceptibility or protection against different types of cancers; and the racial and ethnic distribution of blood groups is an important factor for predicting the cancer risk. The identification of genetic and environmental factors among various racial and ethnic groups along with the use of advanced diagnostic aids in detection of early carcinoma may help for the better understanding of the development, prevention and control of cancer. Blood donation camps can be utilized as a platform wherein when the blood is collected and blood group is recorded, the donors with susceptible blood groups can be counseled and regular cancer screening can be planned for such individuals. Oncology and dental teams should work hand in hand for early detection of cancers. Also, lifestyle modification for giving up tobacco habits and alcohol abuse, if present, needs to be initiated for these individuals. Hence, a widespread team effort is required to utilize the opportunities for prevention of the occurrence of cancer in susceptible blood group.

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