Research Article

ASSOCIATION BETWEEN ABO BLOOD GROUP AND ORAL CANCER - A RETROSPECTIVE HOSPITAL BASED STUDY IN PATNA, BIHAR

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ARTICLE INFO	ABSTRACT
	Introduction: Cancer is a unique disease characterized by abnormal growth of cells which have the ability to invade the adjacent tissues and sometimes even distant organs. In India, oral cancer accounts for about 40 % of all cancers of the body and is a major public health problem, emerging as a killer disease. Cancer in all forms accounts for around 12% of the deaths throughout the world. India has one of the highest incidences of oral cancer in the world. **Aim:** To evaluate the association if any between ABO blood groups and oral cancers. **Methods:** Study was conducted at Mahavir Cancer Sansthan, Patna. It comprised of 300 oral cancer patients and 800 controls. Chi square test and odds ratio were used to assess the association between ABO blood groups and oral cancers. **Results:** It was found that people with blood group A had higher risk of developing oral cancers when compared to people of other blood groups. **Conclusion:** It was observed that different blood group have been associated with oral cancers and blood group A has more predilections for developing oral cancers.

INTRODUCTION

Cancer has been affecting human race since time immemorial[1]. It is a unique disease characterized by abnormal growth of cells which have the ability to invade the adjacent tissues and sometimes even distant organs. If the cancer progresses beyond the stage that it can be successfully removed, it may even result in the death of the individual. Cancer in all forms accounts for around 12% of the deaths throughout the world. The term oral cancer generally refers to carcinoma of oral mucosal, either epithelial or connective tissue in origin. In India, oral cancer accounts for about 40 % of all cancers of the body and is a major public health problem with sufficient morbidity and mortality, emerging as a killer disease[2]. It is seen predominantly in both sexes accounting for one third of all the cancers in South East Asian countries. India has one of the highest incidences of oral cancer in the world, with estimated incidence of 12.48 cases per 1, 00,000 population in males and 5.52 per 1,00,000 populations in females[1].

The increasing number of cancer related morbidity and mortality has been related to its multifactorial etiology, particularly lifestyle factors such as chronic use of tobacco, spicy food, alcohol and smoking[3]. Oral cancer has multifactorial etiology and is significantly associated with risk factors as mentioned above. Many studies have indicated that genetic factors also have an influence on the etiology of cancer as the genes have been implicated in development and progression of oral cancer[2]. 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 [5].

ABO blood group system, identified in 1900, classifies human blood based on the presence or absence of the antigens A and B carried on the surface of erythrocytes. As an easily accessible factor in an individual's genetic makeup, ABO blood groups have been statistically associated with many diseases. During the past several decades, numerous studies ha00ve shed light on the relationship between ABO blood groups and risk of cancer at different sites, but the results were inconsistent. Recent Genome-wide Association Studies (GWASs) have identified single nucleotide polymorphisms (SNPs) mapped to the ABO blood group gene as the top hit for cancer susceptibility out of millions of SNPs rekindling the old fire. Several meta-analyses have been performed and reported significant association between ABO blood groups and cancer at specific sites, including gastric cancer, pancreatic cancer,

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and breast cancer. However, the relationship between ABO blood groups and overall cancer risk still remains unclear[6].

ABO blood group distribution varies in different geographic and ethnic groups, and socioeconomic groups. In India, the ABO blood group frequency is variable, as blood group B ranges from 6% in negritos of Andamans to 48% in Birijas of Bihar, whereas A group is 20%–30% in Western and Eastern Himalayas and B > O > A > AB is the frequency of blood group in North India.[7]

Alcohol, tobacco smoking and nutritional status are well known factors associated with the increased risk of oral cancer. Other possible factors in the development of oral cancer, such as Human Papilloma virus and ABO antigens, are also being researched. Existing researches link these factors with the development of cancer, but the results are different and still only hypothesis which have to be proven. A possible risk marker for the susceptibility to oral cancer is patients' secretor status. Some people posses the ability to secrete blood group substances in the saliva and they are referred to as secretors, whereas others who lack such ability are referred to as non-secretors. It has been demonstrated in a number of earlier studies that the patient's secretor status may probably be a factor influencing the development of systemic oral disease.[8]

Aims and Objectives

To evaluate if any of the ABO blood groups are associated with an increased risk for oral cancer

METHODS

This is a Retrospective study design. Data was obtained from The Mahavir Cancer Sansthan hospital in Patna. Prior to scheduling the study, official permission was obtained from, Heads/Concerned authority of the Mahavir Cancer Sansthan. The proposed study was reviewed by the Ethical committee of Buddha Institute of Dental Sciences and Hospital, Patna and clearance was obtained. It was systematically scheduled to spread over a period of 2 months from July 2015 to August 2015. 300 patients comprising 270 males and 30 females who were histopathologically diagnosed of oral cancer and admitted in the hospital during the 2 month period constituted the cases. ABO blood group system was used. Eight hundred people, 733 males and 67 females who have donated blood at Mahavir Cancer Sansthan hospital, Patna, during the same 2 month period comprised the controls. Data regarding the patient's personal details, blood groups and oral habits were obtained from their case sheets available in the hospital.

Statistical analysis

Data comparison was done by applying specific statistical tests to find out the statistical significance of the comparisons. Chi-square, Fisher's exact test and odds ratio were used to assess the relationship between ABO blood groups and oral cancer. Probability level was fixed at ≤ 0.05.

RESULTS

300 oral cancer patients constituted the Cases among which 270(90%) were males and 30(10%) were females. 800 subjects who have donated blood during the same were considered as control and among them 733(91.6%) were males and 67(8.4%)

were females. Majority (32%) of patients in cases were seen in the age group of 46-55 years while in control group majority (43.9%) is in the 25 years age group. **(Graph1)**
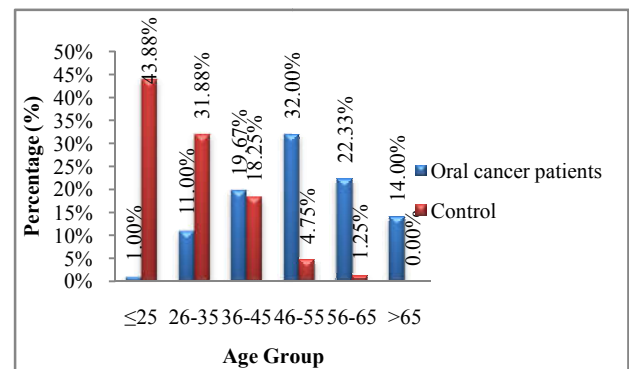
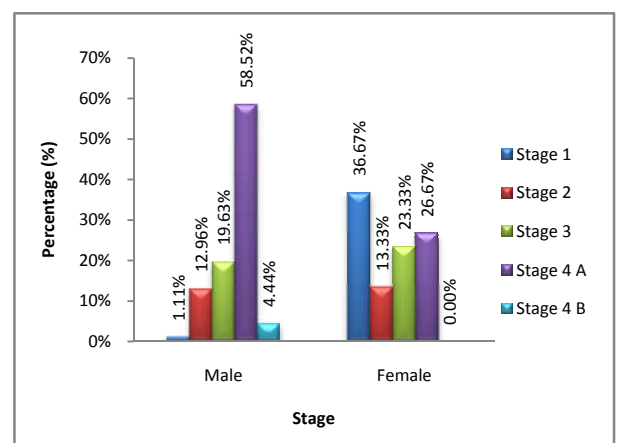**Graph 1** Age wise distribution of Oral cancer patients and Control subjects

Khaini chewing (73.7%) was the most common adverse habit, followed by Gutka use (9.7%). Pan Masala use and use of bidi were seen among 4.3 % and 2.3 % respectively. 10 % of the oral cancer patients did not have any habits.

83.3% of the cases consumed tobacco in the form of smoked less tobacco, while 6.7 % consumed tobacco in smoked form. Results were statistically significant with p value 0.0001.

Squamous cell carcinoma were the most common cancers seen with 94.7%, followed by undifferentiated carcinoma with just 3.7%, less commonly seen were Adenocarcinoma (1.3%) and basal cell carcinoma (0.3%) majority of the squamous cell carcinoma were seen among males (98.1%) when compared to females(63.33).(Table 1)

Table 1 Distribution of Oral cancer patients according to the Types of Cancer

Type of Oral Cancer	Male n (%)	Female n (%)
Squamous cell CA	265 (98.15)	19 (63.33)
Basal cell carcinoma	1 (0.37)	0
Verrucous CA	0	0
Adenocarcinoma	0	4 (13.33)
Malignant melanoma	0	0
Lymphoma	0	0
Undifferentiated CA	4 (1.48)	7 (23.33)
Any Other	0	0
Total	270	30

Graph 2 Distribution of Oral cancer patients according to stage

Majority of oral cancers were seen in buccal mucosa region (34.3%), followed by 21.3% and 19% in Alveolus and tongue region respectively. Soft palate and lip were also affected with 8% and 7.3% respectively.

Majority of the oral cancer were in the Stage 4-A (55.3%), followed by Stage 3 (20%) and Stage 2 (13%), Stage 1 and stage 4-B were 4.7% and 4% respectively. (Graph 2)

Majority of the lesions (35%) were of 2x2 cm in dimensions followed by 3x3 cm and 1x1 cm with 26.3% and 26% respectively, 12.7% of the Cases had lesion exceeding more than 4x4 cm.

Out of 300 oral cancer cases 92 (30.7%) had blood group A, 88 (29.3%) had blood group B, 9 (3%) had AB blood group and 111 (37%) were with blood group O. Among 800 controls 181 (22.6 %) had blood group A, 281 (35.1%) had blood group B, 61 (7.6%) had blood group AB and 277 (34.6%) had blood group O. (Table 2)

Table 2 Blood group characteristics among cases and controls

Subject	Blood Group				Total N (%)
	A N (%)	**B** N (%)	**AB** N (%)	**O** N (%)	
Cases	92(30.7)	88(29.3)	9(3)	111(37)	300(100)
Control	181(22.6)	281(35.1)	61(7.6)	277(34.6)	800(100)
P value	0.006	0.070	0.005	0.462	
	<0.05	>0.05	<0.05	>0.05	

When the case and controls were compared, a significant relationship was found between blood group A and oral cancer. The relative frequency (%) of blood group A was higher in the oral cancer group than in the control group and the difference was statistically significant (<0.005). (Graph 3)
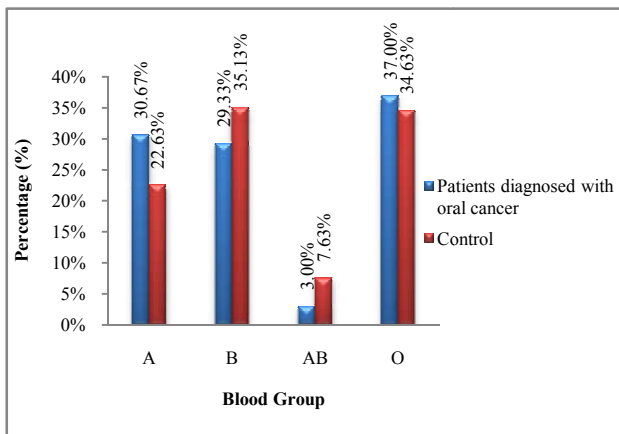
Graph 3 Distribution of Oral cancer patients according to the Types of Cancer

It was observed that people with blood group A had 1.51 times higher risk of developing oral cancer compared to people of other blood groups.

Table 3 Odds ratio showing the strength of association between ABO blood groups and oral cancer

Blood Group	odd ratio (Confidence Intervals)
A	1.51 (1.11-2.05)
B	0.76 (0.57-1.03)
AB	0.37 (0.16-0.77)
O	1.11 (0.83-1.47)

The relative risk was 1.11 for people with blood group O. The relative risk for people with blood group B and blood group AB were 0.76 and 0.37 respectively (Table 3).

DISCUSSION

Oral Cancers have been affecting the human races since time immemorial. The reasons or the patho-physiology are getting better in our understanding with time. This understanding of association between ABO blood group and oral cancers are relatively new, though few studies have been going on for the last few decades. Various theories have been put forth for better understanding of these complexities. But observation studies can only show the direction for exploring the real truth.

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.[2, 11] More than 20 genetically determined blood group systems are known today but ABO 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.[21, 22] In many cancers, the deficiency of A or B epitope has been reported, which is associated with the accumulation of 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.[23]

Blood groups A, B and O were discovered by Karl Landsteinner in 1900 and the 4th group AB was later described by his pupils, Von Decastallo and Sturli in 1902. In this study, among cases, blood group 'O' (37%) was most commonly seen, followed by blood group A and B, 30.7% and 29.3 % respectively. The least common blood group was AB blood group. The findings were similar to the results of Jaleel and Nagarajappa 2015.[2]

The knowledge of association between blood groups and diseases frequencies evolved in the early part of the last century. Since then we have come a long way in the study of association between blood groups and specific diseases, i.e. both systemic and oral diseases.[2, 11]

This study clearly demonstrates that there exists a relationship between ABO blood groups and oral cancers. People having blood group A were found to have a greater tendency to develop oral cancers. 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 glycosyl transferase that is involved in the biosynthesis of A and B antigens is seen in association with tumor development. Studies on carcinomas indicate that events leading to loss of A transferase are related to loss of chromosomal regions including 9q34, which is the locus for the

ABO gene. Thus explains the reason for why it is more frequent among A blood group. The 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 cell surface is a tumor associated change resulting in malignancy.[11] Similar results were seen with studies of Jaleel and Nagarajappa 2012.[2] Other studies, which were done in India, have demonstrated individuals with blood group A have predisposition for oral cancers (Bhateja and Arora 2014;[7] Trupti Dinesh Chordia *et al*., 2015).[11] Studies of Hamed Mortazavi *et al*., 2014; [5] Jyoti R Byakodi and Pushpanjali, 2015;[1] Khusboo Singh *et al*., 2014 [3] showed contrasting results when compared to our results.

H antigen is a blood group antigen present in all the individuals irrespective of blood group types. It is the precursor for the formation of A and B antigens. In people belonging to A and B blood groups, the precursor H antigen is converted to A and B antigens, respectively, whereas in O blood group individuals, it remains in its original form. People with O blood group have the highest amount of H antigen which affords protection against oral cancer. Hence, O blood group people were least susceptible to develop oral cancer.[21]

Assessing the potential risks of the ABO blood groups for the development of various cancers through odds ratio, it was found that blood group A had highest potential of developing oral cancer (1.51, $p<0.05$). These findings are in agreement with the study conducted by Jaleel and Nagarajappa in 2012.[2]

Since this study was a retrospective study, other details about the patient like age, gender, habits and site of oral cancer were available and these data were also analyzed.

In this study, more cases of oral cancer were seen among males (90%) when compared to females. In this region of north east India, use of tobacco (both smoked and smokeless) is more common among males (WHO reports 2015). While in other regions of India like south India, the results are contrary as it is seen more in females, because they consume more spicy food and in addition to this females compared to males have the habit of keeping tobacco in their oral cavity for a longer duration of time. This finding is supported by the report of National Cancer Registry Program conducted by the Indian Council of Medical Research, [17] FDI world report1996 and epidemiological data of Moore *et al*.[18]

In this study, the highest frequency of oral cancers cases irrespective of blood groups was seen in the age group of 36-55 years. This is in accordance with the well proven fact that most cancers of the body occurs around the 4th decade of life.[16] Cawson also suggested that oral cancers is an age related diseases and 98 % of patients are over the age of 40 (Cawson and Odell 2002).[11] Very few cases were seen in the 25-35 years age group. This may be due to the shorter duration of exposure to carcinogens. However, in recent decades an upward trend has been observed in the number of oral cancer case among women and younger age groups (Fazeli *et al*., 2011).[18]

According to our results the incidence of squamous cell carcinoma was more common (94.7%) and it was seen more among males (98%). Similar results were seen with studies of Hamed Mortazavi *et al*., 2014.[5]

The most common site for occurrence of oral cancer was buccal mucosa (36.5%). This is because, majority of the people have a tendency to keep the quid in buccal vestibule, which over a period of time causes chronic irritation to buccal mucosa ultimately resulting in cancer, Other common sites involved were alveolus, tongue, palate and lip, since they are also actively involved in the process of chewing or smoking.(Trupti Dinesh Chordia *et al*., 2015[11] and Jaleel and nagarajappa 2015).[2] Most the cases were in advanced studies(Stage 4A (55.3%), there were no studies to compare with the results of our study.

Tobacco chewing (91%) is generally considered as the primary local etiological factor for oral cancer. Smoking and alcohol merely act as co-factors. The same was reflected in this study, wherein the frequency of the oral cancer was highest among those who had the habit of chewing tobacco. These findings are in agreement with the study conducted by Jaleel and Nagarajappa in 2012.[2]

Limitation and Scope: - Present study reveals a strong association of blood group A with most oral cancer patients, though the actual reason of association of oral cancer with a particular blood group still remains unknown as H antigen is present in all the individuals irrespective of the blood group types. Additionally, it might have nothing to do with molecular mechanism or genetics. However, the limitation of the study lies in the lack of genetic mapping of the subjects. Genetic mapping is required to ascertain the proposed hypothesis. Thus, further longitudinal studies on blood groups in large serious are needed to elucidate and confirm the relationship between blood groups and cancers.

The study results indicate susceptibility of different blood groups for cancers which creates a need to spread awareness among the mass for the same. Early and regular cancer screening should be advised to the patients of susceptible blood groups if any known etiological factors like tobacco or alcohol abuse are noticed or if any sign or symptom of cancer is suspected. They should be trained for self examination and be encouraged for early referrals of cancer screening if in doubt. Public Health professionals should work towards awareness, advocacy and action on health through tobacco cessation programmes, collaborating with other institutions and organizations and meeting the nutritional needs of patients of cancer, other diseases as well as malnourished/undernourished people which are all risk factors for development of cancer. Area volunteers or health workers can be utilized as a part of various outreach programmes who can aid in bringing awareness about the cancer and its preventive methods to people at the local level within their areas, continuous self monitoring and screening of susceptible individuals as well as regular health education can be reinforced as a preventive measure.

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 team 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 comprehensive team effort is required to utilize the opportunities for prevention of the occurrence of cancer in susceptible blood groups.

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