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RESEARCH ARTICLE

MCV- AN EMERGING BIOMARKER IN ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Oral cancers commonly develop in people who consume tobacco in various forms and drink alcohol. They are both independent risk factors, but they have a considerable synergistic effect. Various studies have tried to correlate the role of alcohol alone as a causative factor of oral cancer. But it is difficult to establish principally because alcohol consumption histories are subjective and difficult to verify, alter over time, both with respect to beverage type and quantity, and are frequently confounded by tobacco use. Hence there is a need to develop a more objective way of assessing the chronic intake of alcohol. The mean corpuscular volume or "mean cell volume" (MCV) is a measure of the average red blood cell volume and can be used as an objective indicator of alcohol intake. The aim of the study is to emphasize the role of MCV measurement as a new means of predicting risk for OSCC in Indian population. This is a comparative study in which the MCV is estimated in patients of oral cancer with history of both tobacco and alcohol intake and in patients with history of tobacco and alcohol intake without cancer. This article reviews the role MCV as an objective marker in patients with oral cancer and to find out how effective MCV is in assessing the risk of the disease progression.

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INTRODUCTION

Alcohol consumption and tobacco smoking, both are independent risk factors for oral squamous cell carcinoma (OSCC) of the oral cavity, pharynx, larynx, and esophagus in developed countries. These factors act synergistically and syntactically to increase the oral cancer risk. (Akira Yokoyama *et al*., 2010) The earliest clinical observation associating chronic alcohol consumption with cancer was that of J. C. Warren, Boston surgeon, who in 1836 described a case of lingual cancer in a tobacco chewer by saying, predisposition was generated by the long use of ardent spirits. (Warren, 1976) Since then, various studies conducted in the United States with axiomatic evidence have confirmed that chronic alcohol consumption markedly increases the risk for oral cancer, (Bross and Coombs, 1976; Graham *et al*., 1977; Keller and Ferris, 1965; Rothman and Keller, 1972; Vincent and Marchetta, 1963; Wynder and Bross, 1957; Wynder *et al*., 1957) esophageal cancer (Kamionkowski and Fleshier, 1965; Wynder *et al*., 1957) as well as cancer of the glottis and supraglottis and that this empirical phenomenon applies primarily to users of various forms of tobacco both when smoked and chewed. (Moore, 1965; Schottenfeld *et al*., 1974) Many studies have tried to correlate the role of alcohol alone as a causative factor of oral cancer. (Graham R. Ogden, 2005; La Vecchia *et al*., 2004; Llewellyn *et al*., 2003) But it is difficult to establish principally because alcohol consumption histories are subjective and difficult to verify, alter over time, both with respect to beverage type and quantity, and are frequently confounded by tobacco use. Hence there is a need to develop a more objective way of assessing the chronic intake of alcohol. The mean corpuscular volume or "mean cell volume" (MCV) is a measure of the average red blood cell volume and can be used as an objective indicator of alcohol intake. Increased mean corpuscular volume (MCV) has been used as a biomarker of alcohol abuse for many years in case of esophageal squamous cell carcinoma. (Yu-Zhen Zheng *et al*., 2013; Goodson *et al*., 2010) Hence the aim of the study is to emphasize the role of MCV measurement as a new means of predicting risk for OSCC in Indian population. This is a comparative study in which the MCV is estimated in patients of oral cancer with history of both tobacco and alcohol intake and in patients with history of tobacco and alcohol intake without cancer. This article reviews the role MCV as an objective marker in patients with oral cancer and to find out how effective MCV is in assessing the risk of the disease progression.

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MATERIALS AND METHODS

After the proposed study was reviewed and approved by the ethics committee of the Institute and informed consent been

obtained, 60 patients (30 control group and 30 case group) who presented to the Department of Oral medicine and Radiology at School of Dental Sciences, KIMSDU, Karad were recruited. Control group included 30 patients with habit of either tobacco (betel nut chewing /smoking) or alcohol intake or both with no oral cancer present. Case group included 30 patients with habit of tobacco (betel nut chewing /smoking) and alcohol intake with oral cancer present. Data were recorded about patients' smoking habits, and included the number of cigarettes or ounces of tobacco smoked/day, betel use (amount and number of times a day), and units of alcohol consumed weekly (more than 28 units/week was regarded as a high intake). Information on the patients' drinking and smoking habits, including the date of taking their last alcoholic drink, was obtained from the patients themselves and, when available, their partners. Venous blood samples were obtained from each patient's antecubital vein and placed in an EDTA tube for measurement of MCV, which was done within 2 h. using a reference range for MCV of 80–96 fl, values of over 100 fl were accepted as diagnostic of macrocytosis. Patients were excluded if they had other causes of macrocytosis. MCV was measured using electrical impedance method with an autoanalyzer machine (CELL-DYN 3500, Abbott, North Chicago, IL). The data collected was subjected to statistically analysis and the results obtained are shown in Table 1 & 2.

RESULTS

A total of 60 patients (30 control group and 30 case group) were recruited in the study. Control group included 30 patients with habit of either tobacco (betel nut chewing /smoking) or alcohol intake or both with no oral cancer present. Case group included 30 patients with habit of tobacco (betel nut chewing /smoking) and alcohol intake with oral cancer present. The mean age of occurrence for both the groups is as shown in Table 1. The role of MCV in both the groups was statistically significant with p value of less than 0.0001 and the standard deviation between both the both groups is as shown in table 2.

DISCUSSION

Oral cancer is the third most common cancer worldwide. Its incidence and mortality rates vary widely across the world and highest rates are registered in India, Bangladesh and Pakistan. This difference can be attributed to geographic variation, life style and habits. Tobacco and alcohol consumption are considered to be potential risk factors and act synergistically and syntactically to increase the oral cancer risk. Numerous studies in recent years have tried to correlate the role of alcohol alone as a causative factor of oral cancer. (Graham R. Ogden, 2005; La Vecchia *et al*., 2004; Llewellyn *et al*., 2003) Assessing this potential risk factor in individual patients is

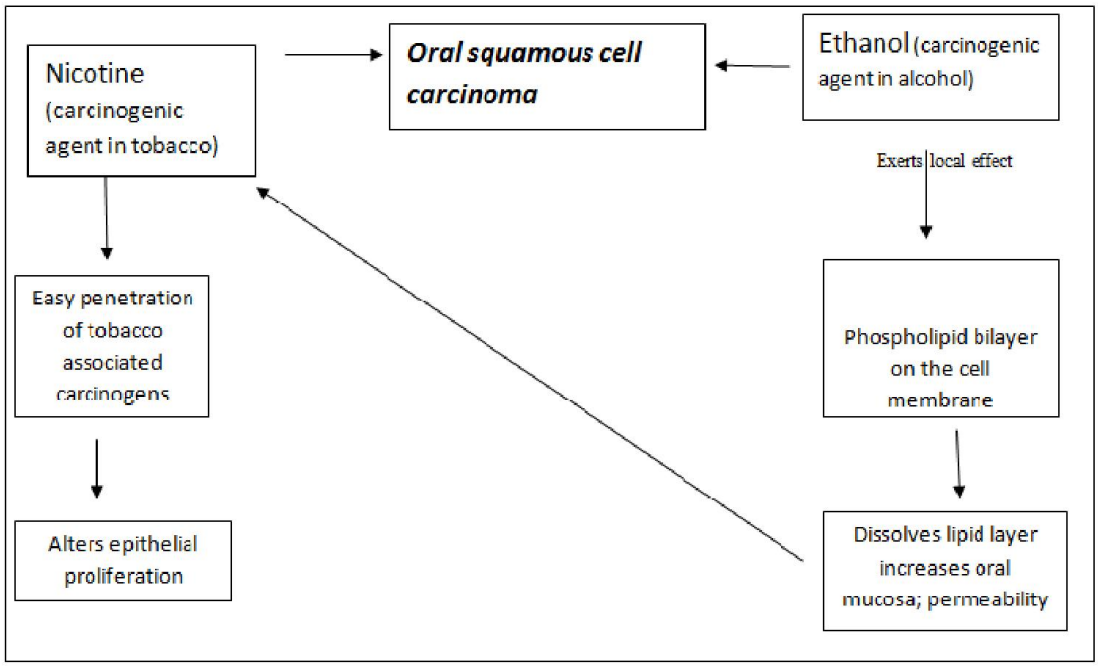

Fig. 1. Diagrammatic illustration of pathway proposed for alcohol associated carcinogenesis (MASEREJIAN 2006)

Table 1. Descriptive data of the study sample

Study Group	Mean Age
Case group	49.6
Control group	43

Table 2. Relation of MCV in both the groups and standard deviation with P value

Study group	Mean (SD)	P Value
Case group	88.85 SD – 8.03	P - 0.0001
Control group	73.68 SD- 15.78	

often based on subjective and possibly unreliable estimates of self-reported alcohol intake confounded by tobacco use in both forms (smoking & smokeless). Several pathways have been proposed for alcohol-associated carcinogenesis. One pathway hypothesizes that as nicotine is carcinogenic agent in tobacco, ethanol is the carcinogenic agent in alcohol. Ethanol exerts a local effect on the phospholipid bilayer on the cell membrane, thus dissolving the lipid layer and increasing the oral mucosal permeability. This in turn facilitates the easy penetration of tobacco associated carcinogens like nitrosamines and polycylic hydrocarbons, which alter epithelial proliferation as shown in Fig. 1. Further damage may be caused by impaired cytotoxin metabolism and inhibition of DNA repair. (Jaber *et al*., 1998; Maserejian *et al*., 2006) Another theory postulates that ethanol is not itself carcinogenic, but is metabolized in the liver by alcohol dehydrogenase to the carcinogen acetaldehyde. In upper aero digestive tract cancers, such as oesophageal carcinoma, case control studies have identified a relation between increased activity of inactive aldehyde dehydrogenase, an enzyme important in the elimination of acetaldehyde, and the development of cancer, particularly in patients with multiple lesions and field changes. (Andre *et al*., 1995) Gastrointestinal microflora may also alter the metabolism of ethanol to create excess acetaldehyde. (Macfarlane *et al*., 1996) Other important systemic effects of alcohol include hepatocellular damage, impaired detoxification, nutritional deficiencies, and immunosuppression. (Maserejian *et al*., 2006) Hence modifying these risk factors are crucial in the management of oral cancer cases. Patients are vague in reporting alcohol intake and smoking, making it difficult to identify which risk factor is responsible. Further evidence is weakened by subjective estimates of alcohol intake from patients and is confounded by their use of tobacco. Objective measures of alcohol intake may be more useful in finding out which patients are at higher risk of malignant transformation. Various traditional objective markers are involved in assessing alcohol consumption such as Gamma Glutamyltransferase, Aspartate Aminotransferase, Alanine Aminotransferase, Mean corpuscular volume. Amongst these, MCV measurement is widely available and is routinely measured during blood investigations and is relatively easy and inexpensive test. Mean corpuscular volume (MCV) is a measure of the average red blood cell volume i.e size of the RBC's and is part of a routine Complete Blood Count (CBC) count done in laboratory. It is calculated by dividing the hematocrit by the red blood cell count (number of red blood cells per litre) and is documented in femtolitres. The normal reference ranges from 80-100 fL. Increase in MCV values are seen in various situations like liver diseases, nutritional deficiencies especially Vitamin B12 as well as in chronic alcoholism that has a direct toxic effect on red blood cell erythropoiesis. (Goodson *et al*., 2010; Hejberg *et al*., 1986) This is the first study wherein MCV is used as an objective marker in patients with oral cancer and to find out how effective MCV is in assessing the risk of the disease progression. Akira Yokoyama *et al* in 2003 inferred that MCV measurement, alone or in combination with the other markers of alcohol sensitivity, provides a new means of predicting risk for Oesophageal Squamous cell carcinoma in Japanese alcoholic men. They evaluated the reliability of MCV testing in combination with the alcohol flushing questionnaire or genotyping of ALDH2 and ADH2 in predicting the risk of esophageal cancer among Japanese alcoholic men and found out that MCV is inexpensive method which can be used as screening tool for early diagnosis which can further be subjected to expensive ALDH2 genotype methods, thus has the potential to serve as a crucial complement in early intervention strategies to control this high-mortality cancer. (Akira Yokoyama *et al*., 2010) Maserejian *et al*. in 2006 noted that an alcohol intake of more than 30 g/day was associated with a 2.5 times increase in the risk of developing a precancerous lesion. He also noted that it increased the relative risk of malignant transformation and these changes were independent of drink or drinking pattern (Maserejian *et al*., 2006) Goodson *et al* in 2010 showed that there was a clear association between alcohol intake and MCV. He concluded that patients who regularly drink a lot of alcohol are at an increased risk of developing further disease after their oral precancerous lesions have been treated. In his study he summarized that consumption of more than 28units/week increases the risk of recurrent disease after treatment and was significantly associated with increased dysplasia at initial presentation. (Goodson *et al*., 2010) Taking into consideration all the above studies, we designed a study wherein the role of alcohol alone in oral cancer was evaluated using the parameter MCV. This study result showed that patients who regularly drink a lot of alcohol are at increased risk of developing further disease after their oral cancer has been treated. The macrocytosis in our patients was considered to be directly attributable to alcohol. We found neither folate nor vitamin B12 deficiencies in our patients at the time of presentation. We also acknowledge that MCV has its limitations as a biomarker, but the lack of any significant difference between subjective and objective (MCV) measures of alcohol intake in this study helps to confirm that patients were probably reporting their intake accurately. We thus conclude that there is a clear need to develop a more objective way of assessing risk, comprising clinicopathological features, profiles of risk factors, and biomolecular markers. This should help clinicians to identify and treat patients at high risk of malignant transformation as soon as possible. Further investigations with larger sample size are required to establish its definitive role. Also relation of MCV with different grades of OSCC should be included so as to see the effectiveness of this parameter that can further influence the prognosis of the disease.

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