

**SALIVARY BIOMARKERS IN ORAL LEUKOPLAKIA-A REVIEW****Dr.T.N.UMAMAHESWARI\***

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**ABSTRACT**

Early diagnosis of oral cancer, which accounts for 3rd most common cancer in Indian population, is essential to improve the quality of life in such patients. Squamous Cell Carcinoma accounts for majority of oral cancer and leukoplakia is one of the most common potentially malignant lesions of the oral mucosa with malignant transformation rate ranging from 0.6 to 20%. There are many invasive & non-invasive diagnostic techniques to assess the malignant risk potential in cancer risk patients. One such non-invasive diagnostic technique to evaluate cancer risk potential in potentially malignant disorders such as leukoplakia is sialodiagnosis. Salivary biomarkers are used in diagnosis of oral & systemic diseases. This article aims in reviewing the various salivary biomarkers in oral leukoplakia to identify the most significant diagnostic & prognostic marker of oral carcinoma.

**KEY WORDS:** Leukoplakia, Oral Squamous cell Carcinoma, Saliva, Biomarker, Diagnosis



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## INTRODUCTION

Cancer is the second most common disease in India responsible for maximum mortality with about 0.3 million deaths/year<sup>1</sup>. In India, the age standardized incidence rate of oral cancer is 12.6/100,000 population and a sharp increase in the incidence rate of this cancer has been reported in recent years<sup>2</sup>. The high incidence of oral cancer in India has also been linked with habits of tobacco chewing & smoking<sup>3</sup>. Potentially malignant lesions of oral mucosa are relatively common, which includes oral leukoplakia, erythroplakia, oral submucous fibrosis etc. Leukoplakia (OLK) is one of the most common potentially malignant lesions of oral mucosa, with a malignant transformation rate in various studies and locations that range from 0.6 to 20 %<sup>4</sup>. OLK is usually diagnosed by the dentist during routine dental examinations. Diagnosis is made based on clinical history and examination of lesion, though biopsy is necessary for confirmation of the diagnosis. Biopsy is an invasive procedure & all patients may not be willing for biopsy as the lesion is usually asymptomatic. Biopsy is the gold standard for cancer diagnosis currently but the process of biopsy has few pitfalls when diagnosing early stage lesions<sup>5</sup>. So, switching on to a more non-invasive diagnostic procedure will be useful in detecting the cases with better patient compliance. There are various non invasive techniques in detecting oral pre-malignancies, which includes vital tissue staining with toluidine chloride, various visualization adjuncts which include ViziLite, Microlux DL system, Orascopic DK system & VELscope system & cytopathology by oral CDx Brush test system<sup>6</sup>. These techniques have been proven to be accurate. But these techniques are expensive and the patients will not be willing to afford for an asymptomatic lesion. Initial studies focused mainly on steroids and antibodies in saliva. Several studies have been conducted to analyze the salivary biomarkers in oral cancer & oral pre-cancer. Till date, many biomarkers have been analyzed in both serum & saliva. There are several body fluids which can be used for diagnostic purposes which include serum, urine, cerebrospinal fluid etc, but Sialodiagnosis has its own advantages as it is

non invasive & is convenient because saliva specimens can be collected with ease. It has been shown that salivary levels of biomarkers are found to be equally sensitive as serum levels<sup>7</sup>. Saliva is acceptable as a diagnostic fluid as it is most available, non-invasive, persistent biofluid of human body<sup>8</sup>.

### AIMS & OBJECTIVES

To find out the most validate salivary biomarker in oral leukoplakia, which will be useful in early diagnosis of oral cancer from potentially malignant disorders, thereby helpful in early treatment of such lesions.

### SEARCH STRATEGY

A systematic search of the literature was done using the Pubmed Database, Medical Subject headings using keywords: "Salivary biomarkers in leukoplakia" & 123 articles were reported. The current review article aims in evaluating the salivary biomarkers that can be used in the early diagnosis of leukoplakia turning into malignancy. Following inclusion & exclusion criteria was devised to evaluate the salivary biomarkers in leukoplakia. Inclusion criteria: Salivary Biomarkers in leukoplakia, & biomarkers in leukoplakia & oral carcinoma. Exclusion criteria: Salivary biomarkers where leukoplakia is not included and only oral carcinoma is studied & salivary biomarkers where other extra oral carcinomas are studied.

## RESULTS

Based on above mentioned criteria 35 articles were selected & were reviewed for selecting the appropriate clinical trials. 23 articles were then determined to be types of studies in which either only oral squamous cell carcinoma (OSCC) were studied or oral carcinoma was compared with pre malignant lesions in general and not leukoplakia in particular. Hence such articles were excluded. In this review article, 12 clinical trials where various salivary biomarkers were tried in OLK are included based on the above mentioned criteria (Table 1).

**TABLE 1**  
**Diagnostic clinical trials of salivary biomarkers in oral leukoplakia**

Year	Journal	Salivary biomarker	Sample size	Results	Remarks
1970	ActaPatholMicrobiolScand	Lactate Dehydrogenase (LDH)	Leukoplakia-29; OSMF-25; OSCC-10; Control-32	Mean isoenzymeratio significantly differed from that of control as well as from that of OLK when compared with OSCC <sup>9</sup>	LDH can be used as a reliable marker.
1984	Boll SocltalBiolSper	Carcinoembryonic Antigen (CEA)	Leukoplakia-12 Control – 14	Not statistically significant <sup>10</sup>	CEA cannot be used as a marker
1992	VoprOnkol	Alkaline phosphatase (ALP), Acid phosphatase, lactate dehydrogenase	Leukoplakia-7 Control – 66 Carcinoma – 100	The activity of LDH & alkaline & acid phosphatase in oral malignancies were 1.5-6 times than in normal mucosa. An increase in LDH & ALP activity was registered for leukoplakia <sup>11</sup>	Can be used as a markers
2006	Oral Oncol	IL -6, TNF $\alpha$	Leukoplakia-30 Control – 34	Significant rise in IL-6 & TNF- $\alpha$ when compared to control <sup>12</sup>	IL-6 & TNF $\alpha$ are not influenced by smoking. Can be used as a useful marker. The alterations in salivary IL-6 & TNF- $\alpha$ might play a significant role in development of oral leukoplakia.
2011	Regulatory peptides	Endothelin – 1(ET-1)		It is not a good marker of OSCC & oral leukoplakia in saliva <sup>13</sup>	ET-1 cannot be used as a biomarker
2011	International Journal of Cancer	$\gamma$ -amino butyric acid (GABA), phenylalanine, valine, n- eicosanide, lactic acid	Leukoplakia-32 OSCC-37 Control-34	Valine, Lactic acid & phenylalanine in combination yielded satisfactory accuracy, sensitivity, specificity & positive predictive values in distinguishing OSCC from the controls or OLK respectively. The salivary levels of GABA, phenylalanine & valine were significantly lower, while n-eicosanoic acid and lactic acid were significantly higher in OSCC group than in Oral leukoplakia & control <sup>14</sup>	Lactic acid & valine are the best predictors from distinguishing OSCC from healthy control, & lactic acid, valine & phenylalanine for OSCC from oral leukoplakia.
2012	J Cancer Research	Lactate	Leukoplakia-25	Leukoplakia-	LDH is a

	Therapy	dehydrogenase	Oral cancer-25 Control-25	136.46±3.36IU/L Oral cancer 148.77±4.83IU/L Control- 79.50±4.67IU/L <sup>15</sup>	Reliable biomarker & it is significantly higher in leukoplakia & even more in Carcinoma.
2012	J Clinical Pathology	Cortisol	Leukoplakia-17 Oral carcinoma- 34 Smokers & drinkers-27 Control-25	P<0.01 <sup>16</sup>	Plasma & salivary cortisol levels are raised in carcinoma.
2012	Journal of the Science & specialization Head & neck	miR-31	Verrucous leukoplakia-10 Oral carcinoma- 45 control-24	Preliminary analysis revealed no significant increase but miR-31 decreased after removal of carcinoma <sup>17</sup>	miR-31 is useful in the early detection of oral cancer.
2012	International Journal of Oral & Maxillofacial Pathology	LDH	Leukoplakia-7, control-7, OSCC-7	The increase in LDH levels was less in saliva as compared to serum in oral leukoplakia. The increase in LDH levels was consistent in saliva & serum of OSCC patients <sup>18</sup>	Salivary LDH is a valuable substitute to serum LDH as a biomarker.
2013	International Journal of Oral Science	Epidermal Growth Factor Receptor 4	Leukoplakia-14, Oral Lichen Planus-10, Control-14	Enhanced expression of ErbB4 on keratinocytes could contribute to the pathogenesis & carcinogenesis of leukoplakia <sup>19</sup>	Keratinocytes in leukoplakia may be more sensitive to stimulation with the ligands for ErbB4, & synchronous modulation of EGFR family genes may be important in the pathogenesis of OLK.
2013	Oxidants and antioxidants in Medical Science	Superoxide dismutase (SOD)	Leukoplakia – 25; OSCC – 25; Control – 25	The mean salivary SOD level in OL, OSCC & Control were found to be 0.52 U/mg, 0.34U/mg & 0.95 U/mg respectively <sup>20</sup>	Consistent decrease in the levels of salivary SOD levels in oral leukoplakia & oral cancer patients when compared to healthy controls. Thus SOD levels could be a useful biomarker in oral carcinogenesis.

## DISCUSSION

Literature review reveals studies in salivary biomarkers for leukoplakia started in 1970's, yet maximum number of studies is being conducted in the last 13 years. Salivary biomarkers have been studied in 208 leukoplakia patients, 283 OSCC patients & 300 controls. Maximum number of leukoplakia patients studied in a study is 32<sup>14</sup> by Jie Wei et al in the year 2011. In 9 trials, marker in leukoplakia is compared with that of OSCC and in 3 trials with controls only<sup>10,12,19</sup>. Many number of studies were conducted in lactate dehydrogenase and studies have proven it can be used a reliable marker for the early detection of OSCC and is reported that Endothelin 1 and Carcinoembryonic Antigen are not significant markers. In a study conducted by Airoidi M et al it was found that determination of the salivary CEA levels are not correlated with CEA serum values, with cigarette consumption and clinical stage<sup>10</sup>. In a study conducted by Hoffmann et al in 2011 it was proved that there was no statistical difference in salivary endothelin-1 levels, neither in OSCC or oral leukoplakia<sup>13</sup>.

## CONCLUSION

Sialodiagnosis like routine hemogram must be employed in all dental institutions to judge the cancer risk potential in each of the potentially malignant disorders to ensure early diagnosis of malignancy for early treatment & better prognosis. To ensure success of sialodiagnosis, standardization of saliva collection & diagnostic procedure is essential.

### AUTHOR'S SUGGESTION

This review article proves the demand for future research study to concentrate on salivary biomarker as a prognostic marker before & after treatment of leukoplakia & in other Potentially Malignant Disorders (PMD). Identification of most validate salivary biomarker to assess cancer risk potential in all PMDs such as erosive Lichen Planus, Erythroplakia, Oral Submucous Fibrosis is essential. More clinical trials need to be conducted in large size samples of leukoplakia including equal number of homogeneous & non homogenous leukoplakia to assess the malignant risk potential in non-homogeneous against homogeneous leukoplakia.

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