

**Rate of Malignant transformation in Leukoplakia: A meta-analysis**

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**Abstract**

**Introduction:** Squamous cell carcinoma of oral cavity is the most common cancer of head and neck region often preceded by any of potentially malignant disorders. Oral leukoplakia is a potentially malignant disorder with an increased risk of oral cancer. Major risk factors associated are tobacco smoking and alcohol intake. Many studies have been published linking the lifestyle changes with malignant transformation. Hence, there is a need to identify the risk factors related with malignant transformation to predict it at the earliest.

**Aim and objective of study:** To generate evidence and to find any correlation on the current malignant transformation rate with other parameters in oral leukoplakia.

**Material and methods:** Meta-analysis was done using previous published data. Articles were searched in Pubmed, EMBASE, Google scholar and Cochrane database.

**Result:** Malignant transformation rate in 1996 was 5.76% which increased to 10.6% in 2018.

**Conclusion:** The two-fold increase in the malignant transformation rate is alarming and adequate steps should be taken in this regard.

**Keywords:** Leukoplakia, oral cancer, malignant transformation, risk factor, dysplasia

**Introduction**

Oral leukoplakia is a common potentially malignant disorder of oral cavity, with a global prevalence rate of 2.60%. [1] It is described as a white patch on the mucosa that cannot be scrapped off or cannot be classified as any other known lesion. All leukoplakias do not transform into malignancy. [2] The malignant transformation rate of leukoplakia depends on factors like site, genetics, habit, gender, age of patient.

The histopathology of leukoplakia varies from atrophic epithelium to hyperplasia with or without hyperkeratosis and dysplasia. [3] The presence of moderate to severe dysplasia suggests greater risk for

malignant transformation. Currently epithelial dysplasia is a predictive indicator for malignant transformation. [4] Major indicators of malignant transformation are p53 gene mutation, loss of heterozygosity and chromosomal polysomy are major indicators of malignant transformation. [5]

### **Material and Method**

A search was conducted in PubMed database. The search included potentially malignant disorders, oral leukoplakia, risk factors and dysplasia.

### **Selection criteria**

Articles published in English language were evaluated using titles and abstracts, and only those articles which matched study criteria were included. Observational and case control studies were included. Journals articles with Systematic reviews published were given preference. Case report, clinical trials, letter to editor, experimental studies, and studies with incomplete data were excluded. Data selection was as per the guidelines of PRISMA (Preferred reported items for systematic reviews and meta-analysis).

### **Results and Statistical analysis**

40 studies fulfilled the inclusion criteria. 27 studies were excluded (irrelevant data, incomplete studies, inappropriate subject selection). 13 studies were finally included in meta-analysis. The statistical analysis was done using SPSS version 21. Data distribution was assessed using Shapiro–Wilk test. Categorical data were analyzed by Chi-square test.  $p < 0.05$  was considered statistically significant.

The earliest study was done in 1967 by Einhorn et al. [6,7] The recent study recorded with a follow up of 7 years was by Jasbir et al in 2018. [8] The largest study was done in 1976 by Silverman on 4762 leukoplakia cases observed for 2 years. [9] The malignant transformation rate was calculated using ANOVA.

Significant differences in malignant transformation rate were observed based on follow-up (p-value: 0.04). The mean malignant transformation rate of leukoplakia for 5 years follow up is 4.6%, 5-10 years is 28.1 % and after 10 years it is stabilized at 26.2%.

Data on predominant site was collected from 15 articles. Highest rate was associated with tongue followed by gingiva and buccal mucosa.

There is an increase in malignant transformation rate of leukoplakia from 20<sup>th</sup> century. It was only 5.76% till 1996, but it was 10.9% in 2018. This 2-fold increase is due to many factors like genetic mutations, food habits, increased smoking habits in females, stress, lifestyle changes and altered work period.

### **Discussion**

Meta-analysis is a statistical, epidemiological, quantitative study design used to systematically assess the results of previous research to derive reliable conclusions about that body of research.

They are different from conventional studies. It is a study of various studies on a particular topic. Outcome from a meta-analysis provide a more accurate estimate of the treatment or risk associate with disease, or any other result than any individual study.

Term Leukoplakia was first reported in 1877 by Erno Schwimmer in 1877. [2] The incidence of leukoplakia is 0.2% and prevalence is 4.9%. [10] Leukoplakia occurs mostly in older age group above 40 years of age. [11], [12] The principle risk factors for oral leukoplakia are tobacco usage, smoking and alcohol consumption.

A study by C-H Lee et al. found that usage of tobacco significantly increases risk of oral cancer. [4] A fourfold increase in malignant transformation rate of leukoplakia showing severe dysplasia was observed in a study done by Liu et al. on Chinese patients. [10] This

is similar to the present study showing 54% chances of malignant transformation.

The overall malignant transformation rate in patients with leukoplakia is 10.6%. Bzark et al. in his study observed malignant transformation rate of 1.9%.[11] Zakrzewska et al. in his study in London observed the maximum malignant transformation rate.[12] The result in our analysis are similar with many previous studies conducted.

In our analysis we have observed notable trend in malignant transformation rate of Leukoplakia. Malignant transformation rate was 5.7% till 1996, but the rate has increased by two-fold to 10.9% by 2018. According to Gandara-vila et al, the current malignant transformation rate of leukoplakia in 2018 is 8.2% and study by Andrea Rubert et al., in 2020 is 8.3%. This is related to genetic variations, increased smoking in females, lifestyle and food habits and increased stress. [13, 14, 15]

#### **Limitations of study:**

Large studies with long term follow up are required for assessing the prognosis for preventing progression to oral squamous cell carcinoma.

Studies published only in English literature were included for meta analysis.

#### **Conclusion**

The 2-fold rise in the malignant transformation rate from 90s is matter of concern and required steps should be taken in regard to this.

Follow-up studies should be done with cases under each category and malignant transformation in that category should be mentioned. Also the lesions that have regressed or disappeared completely should be included to check the features of these lesions.

In-depth screening should be done in order to assess the dysplastic nature of the lesion and to investigate the

malignant transformation as early as possible. Oral health programs should be conducted in order to bring awareness among people about the detrimental effects of leukoplakia on oral cancer. [16]

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