

Prevalence and Malignant Transformation Rate of Oral Erythroplakia Worldwide - A Systematic Review

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Abstract

Background: To determine the characteristics of oral erythroplakia (OE) on a global scale, it is important to analyse and evaluate findings from various studies conducted across multiple geographical locations. **Objectives:** This review was conducted to determine the prevalence and malignant transformation rate (MTR) of OE. **Data Sources:** A systematic search was performed to identify studies reporting the prevalence and MTR of OE across various databases – PubMed, Web of Science, Google Scholar, Elsevier and ScienceDirect without any restriction for the time of publication. **Study Eligibility Criteria:** This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines, and the protocol was registered in the PROSPERO database (ID: CD42023395215). **Results:** The prevalence rate of OE reported across the studies ranged from 0.04% to 1.14% with a mean of $0.25 \pm 0.002\%$. The MTRs reported across the studies included ranged from 2.6% to 65% with a mean of $30 \pm 0.2\%$. **Limitations and Conclusions:** Based on the findings from the present review, it can be concluded that while the range of MTRs of OE varies widely across different geographical locations, the average rate can be considered 30%. The review also identified a need for conducting more studies on the prevalence rates as well as longitudinal studies assessing the MTR across different regions.

Keywords: Erythroleukoplakia, leukoplakia, oral potentially malignant disorders, premalignant lesions

INTRODUCTION

Oral squamous cell carcinoma (OSCC) has always been one of the leading causes of morbidity and mortality. According to recent GLOBOCAN 2020 data, oral cancers contribute to 10.3% of all cancers in India.^[1] OSCC is a cumulative result of numerous biochemical, genetic, epigenetic and molecular alterations both within the squamous cell epithelium and within the connective tissue stroma.^[2] In about 80% of cases, OSCC is preceded by prodromal conditions, which have been collectively referred to as ‘oral potentially malignant disorders’ (OPMDs).^[3] Amongst the OPMDs, oral leukoplakia (OL) is common, and when interspersed with red areas, it is called oral erythroleukoplakia (OEL).^[3] Oral erythroplakia (OE), which is the completely red counterpart of OL, is defined as ‘A fiery red patch that cannot be characterised clinically or pathologically as any other definable disease.’^[4] Clinically OE presents as well-defined, red velvet areas of ‘angry’ appearance.^[5]

OE is extremely rare in the Western population and its prevalence rate in Southeast Asia has been approximately

reported as 0.02%.^[6] Although less prevalent, OE exhibits a much higher potential for malignant transformation as compared to OL.^[7] The potential malignant transformation rate (MTR) for OE has been reported to be even higher ranging from 75% to 90%.^[8] Various cross-sectional and longitudinal studies conducted to understand the clinicodemographic profile of the regional populations affected by OE provide only locoregional information about the disease.^[7] Thus, the present systematic review was conducted to analyse the prevalence and MTR of OE reported across various studies globally.

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MATERIALS AND METHODS

The present systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines, and the protocol was registered in the PROSPERO database (ID: CD42023395215). A systematic search was performed to identify studies reporting the prevalence and MTR of OE as of March 2022 without any restriction for the time of publication. The keywords used included ‘malignant transformation’, ‘prevalence’, ‘erythroplakia’, ‘erythroleukoplakia’, ‘oral potentially malignant disorders’ and ‘leukoplakia’. Boolean operators (NOT, AND and OR) were also used in succession to broaden the search. The search was performed across the databases – PubMed, Web of Science, Google Scholar, Elsevier and ScienceDirect. The references of the included articles were also scanned to further identify potential studies that could have been missed during the search. The criteria used for the selection of studies are described in Table 1, while the selection process of the studies included in the final analysis is described in Figure 1.

The articles were first screened based on their title and abstract, of which only relevant studies were selected. Full texts of these selected studies were again reviewed based on the above-mentioned selection criteria. Two independent reviewers screened the literature search and assessed each study for inclusion. Any disagreement was solved by consulting a third investigator and mutual agreement. Afterwards, the same reviewers extracted data from the included studies consisting of authors, year of publication, country, sample size, habit, type of lesion, gender, number of cases of OE, type of population, prevalence and MTRs. The quality of the included cohort study was evaluated based on the Newcastle–Ottawa Scale (NOS), and accordingly, a numeric score (NOS score) was assigned. The NOS uses a nine-star rating system with a maximum of four points available for selection, two for comparability and three for the assessment of the outcome or exposure. A study with a score from 7–9 will be considered high quality, 4–6 will be considered moderate quality and 0–3 will be considered low quality or very high risk of bias.

RESULTS

A total of 21 articles were included in the present systematic review. The extracted data from studies reporting the

prevalence of OE are summarised in Table 2,^[9-19] while those concerned with MTRs are summarised in Table 3.^[20-29] The MTRs reported across the studies included in the present systematic review ranged from 2.6% to 65% with a mean of 30% + 0.2%. The wide range of the reported MTRs is attributable to the differences in the study design, selection criteria and methods of reporting used by different authors. The follow-up period in these studies ranged from 18 to 86 months with a mean of 57.93 + 21.56 months. An adequate follow-up period in longitudinal studies is essential for a more precise assessment of the MTR of any OPMD. Chuang *et al.*, demonstrated that the risk of malignant transformation of OPMDs varied by subtype from the lowest risk in OL to, intermediate risk in OSF, erythroleukoplakia and erythroplakia, to the highest risk of exophytic verrucous hyperplasia.^[26] Chiu *et al.*, reported a transformation rate of 3.91% in 5 years and an annual malignant transformation of 9.75/1000 person-years.^[29] Silverman *et al.*, reported that the MTR is fourfold in non homogenous as compared to homogenous leukoplakia after a 7-year follow-up.^[20]

Only one study^[14] gained the maximum score in the selection criteria and was considered to have the highest level of quality with an estimated low risk of bias; four studies^[13,14,17,22] had the maximum score in the comparability outcome and was considered to have the highest level of quality with an estimated low risk of bias, and all the studies had a partial score in the exposure–outcome while only two studies had the highest score for exposure–outcome having the lowest level of quality with an estimated high risk of bias. For the included studies, only two studies^[23,27] reached the maximum score of the NOS. Three studies^[9,23,27] gained the maximum score in the selection criteria and were considered to have the highest level of quality with an estimated low risk of bias; for the comparability criteria, almost all the studies reached the highest score, while for the outcome criteria, only two studies^[23,27] gained the maximum score of 3.

For the included studies, none of the studies reach the maximum score of the NOS. Only four studies^[10,14,19,29] gained the maximum score in the selection criteria and were considered to have the highest level of quality with an estimated low risk of bias; for the comparability criteria, almost all the studies reached the highest score, while for the outcome criteria, only

Table 1: Criteria used for the selection of studies in the present systematic review

	Inclusion criteria	Exclusion criteria
Population (P)	Patients with OE and OEL	Patients with homogenous OL, lichenoid lesions or other similar lesions
Intervention (I)	Patients undergoing malignant transformation within the follow-up period of the study	Studies not confirming the malignant transformation
Comparison (C)	Patients not undergoing a carcinomatous transformation during the period of study.	Studies not following up the patients for malignant transformation
Outcome (O)	Prevalence rate Malignant transformation rate	Relative risk Combined rates of OE/OEL along with other subtypes of OL
Studies (S)	Case–control, cross-sectional and cohort studies	Reviews, case reports and case series, animal studies

OE: Oral erythroplakia, OEL: Oral erythroleukoplakia, OL: Oral leukoplakia

two studies^[15,21] were assigned. The included study had all the low risk of bias. The risk of bias is depicted in Table 4.

DISCUSSION

The presence of a red mucosal lesion persisting for over two weeks after eliminating potential causes should raise concern for the clinician. However, data on the current prevalence and MTRs of erythroplakia are scarce. To address this gap, we conducted a systematic review of 21 manuscripts examining the prevalence and MTRs of OE worldwide. The prevalence rate of OE reported across the studies included in the present review ranged from 0.04% to 1.14% with (mean: 0.25 + 0.002%). Considering the fact that the prevalence of OE is high in Southeast Asian countries, half of the studies ($n = 10$) were reported from this region, of which four were from Taiwan and three were from India. While tobacco consumption in smoking or smokeless form has been regarded as the main risk factor for OL, drinking alcohol along with

chewing tobacco or betel nut has been implied for OE.^[30-32] The 7-year cumulative transformation rate for leukoplakia and erythroleukoplakia was found to be 10% and 65%, respectively, by Yen *et al.*^[24] The authors also found that the relative risk of non-homogeneous leukoplakia/homogeneous leukoplakia was 6.5. It has been observed that about 40% and 9% of cases of OE exhibit mild and moderate dysplasia, respectively, on the first biopsy.^[33] On the other hand, a report from The Netherlands stated that more than 90% of the patients had already developed OSCC (40% carcinoma *in situ* and 51% invasive carcinoma).^[34] In the study by Queiroz *et al.*, OE developed in more than 72% of the cases diagnosed as moderate and severe epithelial dysplasia or squamous cell carcinoma.^[16] Prediction of the risk of malignant transformation is very useful for the health education of betel quid chewers to discourage them from continuing the habit. Chuang *et al.*, found that the risk of malignant transformation ranged from the lowest in OL (5.4/1000) to the highest in OE (11.8/1000) and exophytic verrucous hyperplasia (33.0/1000).^[26] Findings from all the included studies have highlighted the fact that special attention must be paid to such lesions as they represent a warning about the possibility of an existing carcinoma. The tongue and the floor of the mouth have been reported as the most common sites for malignant transformation of OE; thus, erythematous lesions at these sites should raise caution on the part of clinicians.^[6,33]

Because most cases of OSCC are preceded by OPMDs, identifying the latter at the earliest is of utmost importance as the condition can yet be reversed.^[34] Despite the importance of early identification, the lesions go unnoticed in many cases, particularly if they are asymptomatic. Dental professionals play a key role in identifying the lesions and meticulously distinguishing them from other red and white lesions of the oral cavity including erythematous candidiasis, local irritation, mucositis, lichen planus, lichenoid reactions, lupus erythematosus, chemical burns, median rhomboid glossitis, morsicatio buccarum and nicotinic stomatitis.^[6,33] The average time period required for the transformation of an OPMD to malignancy is termed ‘average dwelling time’ (ADT). The longer the ADT of an OPMD, the more likely it is to get detected before its transformation into carcinoma.^[24,35] Furthermore, ADT also provides insight into

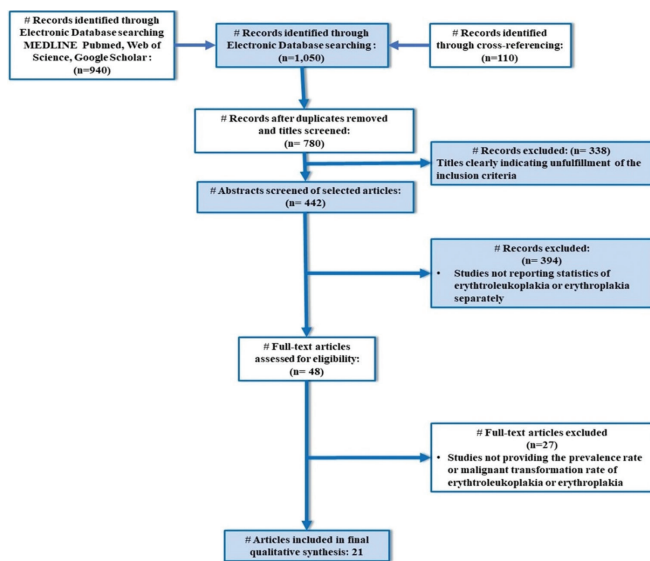


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart indicating the selection process of the articles included in the present systematic review

Author	Year	Country	Type of population	Sample Size	Number of OE cases	Prevalence (%)
Shafer and Waldron ^[9]	1975	Atlanta, United States	Specimen	65,354	58	0.04
Lay <i>et al.</i> , ^[10]	1982	Burma	Villagers	6000	5	0.10
Barrios Sánchez <i>et al.</i> , ^[11]	2007	Cuba	Patients	527	6	1.14
Lapthanasupkul <i>et al.</i> , ^[12]	2007	Thailand	Patients	7177	9	0.13
Silveira <i>et al.</i> , ^[13]	2009	Brazil	Patients	7725	20	0.34
Warnakulasuriya <i>et al.</i> , ^[14]	2010	India	Office workers	2340	1	0.06
Yang <i>et al.</i> , ^[15]	2010	Taiwan	Subjects with oral habits	2020	3	0.15
Queiroz <i>et al.</i> , ^[16]	2014	Brazil	Patients	6560	11	0.16
Kumar <i>et al.</i> , ^[17]	2015	India	Inhabitants	1241	3	0.24
Ferreira <i>et al.</i> , ^[18]	2016	Brazil	Farm workers	1385	4	0.30
Mishra <i>et al.</i> , ^[19]	2019	India	Women in slum areas	11,768	12	0.10

OE: Oral erythroplakia

Table 3: Malignant transformation rate reported across various studies included in the present review

Author	Year	Country	Sample size	Number of OE cases	Follow-up time (months)	MTR (%)
Silverman <i>et al.</i> , ^[20]	1984	US	257	128	86	23.40
Amagasa <i>et al.</i> , ^[21]	1985	Japan	12	10	82	50
Lumerman <i>et al.</i> , ^[22]	1995	US	308	37	18.4	32.40
Sudbø <i>et al.</i> , ^[23]	2002	Norway	37	37	53	62
Yen <i>et al.</i> , ^[24]	2008	Taiwan	8360	124	84	65
Brouns <i>et al.</i> , ^[25]	2014	The Netherlands	144	79	51.2	2.60
Chuang <i>et al.</i> , ^[26]	2018	Taiwan	8501	188	67	11.80
Jayasooriya <i>et al.</i> , ^[27]	2020	Sri Lanka	93	38	30	15.70
Gilveti <i>et al.</i> , ^[28]	2021	UK	95	15	47.7	33.33
Chiu <i>et al.</i> , ^[29]	2021	Taiwan	11594	587	60	3.91

OE: Oral erythroplakia, MTR: Malignant transformation rate

Table 4: Quality score for the included articles using the Newcastle–Ottawa Scale

Author, year	Case-control studies			Overall quality score (maximum=9)	Quality of study
	Selection (maximum=4)	Comparability (maximum=2)	Exposure (maximum=3)		
Lumerman <i>et al.</i> , 1995	**	**	**	6	Moderate
Laphanasupkal <i>et al.</i> , 2007	***	*	**	6	Moderate
Silveria <i>et al.</i> , 2009	**	**	***	7	Moderate
Warnakulasuriya <i>et al.</i> , 2010	****	**	***	9	High
Queiroz <i>et al.</i> , 2014	**	*	**	5	Moderate
Kumar <i>et al.</i> , 2015	**	**	**	6	Moderate
Cohort studies					
Shafer <i>et al.</i> , 1975	****	**	**	8	High
Silverman <i>et al.</i> , 1984	***	**	**	7	Moderate
Sudbo <i>et al.</i> , 2002	****	**	***	9	High
Yen <i>et al.</i> , 2008	**	**	*	5	Moderate
Karagozoglu <i>et al.</i> , 2013	**	**	**	6	Moderate
Chuang <i>et al.</i> , 2018	***	**	**	7	Moderate
Jayasooriya <i>et al.</i> , 2020	****	**	***	9	High
Gilveth <i>et al.</i> , 2021	***	*	**	6	Moderate
Cross-sectional studies					
Mehta <i>et al.</i> , 1982	****	**	**	8	High
Sein <i>et al.</i> , 1982	****	**	**	8	High
Amagasa <i>et al.</i> , 1985	***	*	***	7	Moderate
Yeng <i>et al.</i> , 2010	**	**	***	7	Moderate
Ferreira <i>et al.</i> , 2016	**	**	**	6	Moderate
Mishra <i>et al.</i> , 2019	***	**	**	7	Moderate
Chiu <i>et al.</i> , 2021	****	**	**	8	High

Significance of all asterisk - It denotes newcastle ottawa scale score (*- score 1, **- score 2 and so on). It depicts statistical significance

how frequently early detection of OPM is adequate to stop malignant transformation in an efficient way. The ADTs for OL and OE have been estimated to be 24 and 7 years, respectively. Therefore, in contrast to the other OPMDs, OE provides relatively much less window for diagnosis before transformation to carcinoma. The MTRs of the various OPMDs including OE are not absolute but are rather dependent on various genetic, geographic and lifestyle factors.^[29,35] Stratification of patients with OE on the basis of these factors may facilitate the development of follow-up measures and optimisation of treatment strategies, thus limiting malignant transformation. Although the prevalence of OPMDs is reported to be higher in

Southeast Asia,^[36,37] there are hardly any longitudinal studies reported in the literature from this region.

CONCLUSION

Based on the findings from the present review, it can be concluded that while the range of MTRs of OE varies widely across different geographical locations, the average rate can be considered 30%. Stratification of patients with OE on the basis of these factors may facilitate the development of follow-up measures and optimisation of treatment strategies, thus limiting malignant transformation. The review also identified a need

for conducting more studies on the prevalence rates as well as longitudinal studies assessing the MTR across different regions.

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Conflicts of interest

There are no conflicts of interest.

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