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MALIGNANT TRANSFORMATION OF ORAL SUBMUCOUS FIBROSIS - A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

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ABSTRACT

Oral submucous fibrosis (OSMF) is a potentially premalignant oral lesion. The disorder is insidious and chronic in nature. It has the potential to transform into oral squamous cell carcinoma (OSCC), the rate at which it may happen is described by the term Malignant Transformation rate (MTR). Different studies in various populations have reported varying rates of malignant transformation for OSMF. This study aims to establish the malignant transformation rate of OSMF and to record associated risk factors. The search was performed using MeSH terms and keywords in electronic databases PubMed, Cochrane, Science Direct, and Google Scholar. Out of 190 articles obtained from the initial keyword search, 7 articles were chosen after applying the inclusion and exclusion criteria. The overall malignant transformation rate of OSMF was found to vary from 3.72 – 38.15 % across the 7 studies reviewed in this study with betel quid chewing being the associated risk factor favoring the transformation to oral cancer. The results revealed a higher malignant transformation rate compared to the frequently quoted values. Hence, clinicians need to manage such lesions with utmost care and must subject them to biopsy fo ruling out dysplasia/malignancy. The number of follow-up studies assessing the malignant transformation of OSMF, especially in the Indian population was scarce in the literature highlighting the need for more research in this area.

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Introduction

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, precancerous condition affecting the oral mucosa and pharynx and was first described in the year 1952 [1]. The main etiological agent causing OSMF has been established as arecoline in areca nut [2]. The characteristic clinical features of the disease include pallor of the mucosa, burning sensation, leathering mucosa, and progressive fibrosis resulting in limited mouth opening causing difficulty in speech and swallowing [3]. Areca nut chewing is now the fourth most common addiction habit globally [4]. It is used in various combinations along with betel quid, tobacco, and slaked lime. There are many regional variations within India as well as between different countries [5].
Malignant transformation rates (MTR) of OSMF have been assessed by many researchers in various studies and different populations. One study reported an MTR of 7.6% after a long 17-year follow-up whereas another study from India reported a 2.6% transformation rate [5]. The highest value reported in the Indian population was that of 7.6% by IARC [6]. Assessing the risk status of potentially malignant disorders like OSMF is crucial for a clinician for timely diagnosis and intervention thereby helping provide a better quality of life for these patients. Hence, we aimed to conduct a systematic review to assess the MTR of OSMF and to record the associated risk factors.

Materials and Methods

Ethical clearance was obtained from the scientific review board, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Chennai. Studies published from the year 2014 to 2019 were searched for in electronic databases of

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PubMed, Cochrane, Science Direct, and Google Scholar. All observational follow-up studies on OSMF patients recording MTR, follow-up studies on OPMD that include OSMF and its MTR, and studies on MTR of OSMF / OPMD on any population were included for review. Interventional studies on OSMF/OPMD studies not following the observational study design, follow-up studies on OSMF without assessing MTR, and studies on OPMDs other than OSMF were excluded.

Results and Discussion

The included studies were studied for the overall MTR and annual malignant transformation rate (ATR) values **(Table 1)**. Out of a total of 5043 lesions/ cases of OSMF followed up in all the seven included studies 706 lesions/ cases transformed into malignancy. Malignant transformation in terms of type, frequency, and duration of habits **(Table 2)** was recorded. Quality assessment of the included studies was done using the BSA Medical Sociology Group tool for cross-sectional studies.

Table 1. Characteristics of included studies – Malignant transformation rate

Author, Country, Year	Study Type	Clinical Grading of OSMF	Number of cases/ lesions followed up	Follow-up duration- mean years (range)	Number of cases/lesions with malignant transformation (n)	Overall malignant transformation %	Annual Transformation Rate (ATR)
Chuang *et al*., Taiwan, 2018	P/ C	N/A	2,333	5.7	114	7.69 % [76.9 per 1,000 (cumulative risk in 9 years)]	8.6 per 1,000
Yang *et al*., Taiwan, 2017	P/H	N/A	778	6	71	9.13%	NA
Chien-Yang Yeh *et al*., Taiwan, 2016	P/H	N/A	9	10	1	11%	NA
Mohiuddin *et al*., Pakistan, 2016	P/H	N/A	765	8	472	38.15%	NA
Jayasinghe etal., Sri Lanka, 2015	R/H	Yes	135	5.26	8	5.90%	NA
Nayak *et al*., India, 2015	R/H	N/A	29	3.16	3	10.34%	NA
Wang *et al*., Taiwan, 2014	R/H	N/A	994	9	37	3.72%	NA

P- Prospective study, R- Retrospective study, H- Hospital-based, C- Cohort

Table 2. MTR and Risk habits

Author, Country, Year	Habit & Malignant Transformation						
	Habit Groups			Frequency of habits		Duration of habits	
	Groups	Sample	MT (%)	Frequency	MT (%)	Duration	MT(%)
Chuang *et al*., Taiwan, 2018	1. Ever Betel nut chewing 2. Ever cigarette smoking 3. Ever alcohol drinking 4. Betel nut chewing & cigarette smoking 5. Betel nut chewing & alcohol drinking 6. Cigarette smoking & alcohol drinking 7. Having three habits	2013 2138 1539 572 113 110 1316	8.9% 8.4% 10.0% NA NA NA NA	NA	NA	NA	NA
Yang *et al*., Taiwan, 2017	NA	NA	NA	NA	NA	NA	NA
Chien-Yang Yeh *et al*., Taiwan, 2016	1.Alcohol 2.Betel 3.Smoking	NA	NA	NA	NA	NA	NA
Mohiuddin *et al*., Pakistan, 2016	1. Areca nut only 2. Betel quid with tobacco 3. Betel quid without 4. tobacco 5. Naswar 6.No habits	NA	22.9% 48.3% 11.7% 7.6% 9.5%	NA	NA	NA	NA
Jayasinghe *et al*., Sri Lanka, 2015	1.Areca nut only 2.Betel quid Betel quid only Betel quid & smoking Betel quid & alcohol Betel, smoking, alcohol	5 130 80 10 21 19	0.0% 50.0% 12.5% 12.5% 25.0%	< 5 quids/d 5-10 quids/d 11-15 quids/d 16-20 quids/d >20 quids/d	33.3% 33.3% 33.3% 0.0% 0.0%	0-5 yrs 6-10 yrs 11-15 yrs 16-10 yrs 21-15 yrs >25 yrs	0.0% 16.7% 0.0% 83.3% 0.0% 0.0%

Nayak *et al*., India, 2015	1. Tobacco chewing 2. Alcohol 3. Smoking	NA	NA*	NA	NA	NA	NA
Wang *et al*., Taiwan, 2014	Alcohol drinking Betel quid chewing Cigarette smoking	728 879 857	NA*	NA	NA	NA	NA

This review attempted to establish the MTR of OSMF from observational studies in the literature. An earlier hospital-based study done in the Taiwanese population estimated the MTR to be 7-13 % which is frequently cited [7]. But we found a wider range of MTR of OSMF patients, 3.72- 38.15% across the 7 studies done in varied populations. Wang *et al*. [8], reported the lowest overall MTR (3.72%), followed by Jayasinghe *et al*. [9], (5.90%), Chuang *et al*. [10] (7.69%), Yang *et al*. [11] (9.13%), Nayak *et al*. [12] (10.34%) and Chien – Yang Yeh *et al*. [13] (11.0%). The highest as well as a significantly differing MTR of 38.15 % was reported by Mohiuddin *et al*. [14]. It was a multicenter study conducted at public and private tertiary hospitals and clinics in Pakistan that enrolled 765 cases of OSMF, more than one-third of which transformed into OSCC (472 cases) during a mean follow-up period of 8 years. For the rest of the studies, the follow-up period ranged from 3.6 years to 10 years. The annual transformation rate (ATR) is a valuable guide to the oral medicine specialist since it takes into account the individual time for transformation into cancer [15]. In our review, a single study done by Chuang et el., reported the ATR value as 8.6 per 1000 while the remaining studies assessed only the overall transformation rate [10].
The association of OSMF with betel quid and areca nut chewing, and the increasing incidence of oral cancer in this group has been reported for long [16-18]. The combined use of betel quid and tobacco has been reported to have carcinogenic potential in a dose-dependent way [19]. Jayasinghe *et al*. grouped the patients mainly into two based on chewing habits areca nut chewers and betel quid chewers [9]. Betel quid chewers were further grouped based on additional habits of smoking, alcohol, or both. The highest MTR was seen to be associated with the group with betel quid chewing habit alone whereas none of those in the areca nut chewing group underwent a malignant transformation. Mohiuddin *et al*. have considered chewing habits classifying risk habits into areca nut, betel quid with tobacco, betel quid without tobacco, naswar, and no habits group and have excluded cigarette smoking and alcohol [14]. They reported the MTR to be highest in the betel quid with the tobacco group followed by areca nut chewers. An ideal grouping of risk habits is seen in the study by Chuang *et al*. who grouped the patients based on single habits as well as various combinations of multiple habits which will aid in assessing the habit combination most susceptible to malignant transformation. Unfortunately, the study has not recorded the MTR for the multiple habit groups [10]. The frequency and duration of the risk habits are consequential in the transformation of an OSMF case into OSCC. But only one of the included studies has recorded these aspects of the risk habits to assess their role in MTR. Jayasinghe et. al. grouped the betel quid chewers based on the number of quids per day and habit duration ranging between 0 and 25 years or more. Their observations suggested no significant differences in MTR with frequency [9].

Conclusion

The overall MTR of OSMF varies from 3.72 – 38.15 % across the 7 studies reviewed in this study. Betel quid chewing was found to be a habit with higher chances of malignant transformation.

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