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A Systematic Analysis of Observational Research on the Malignant Transformation Rate in Oral Submucous Fibrosis, an Oral Potentially Malignant Disorder

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Abstract

Oral submucous fibrosis, which is considered a potentially malignant disorder, progresses gradually and often goes unnoticed due to its subtle onset. This chronic condition carries a measurable risk of developing into oral squamous cell carcinoma, a risk quantified through what is known as the malignant transformation rate. The reported figures for this transformation have varied widely across different demographic and clinical studies. To further investigate this issue, the present review systematically evaluated observational studies to assess the malignant transformation rate associated with oral submucous fibrosis and to pinpoint contributing Risk factors. A detailed database search was executed using MeSH terms and targeted keywords within PubMed, Cochrane, Science Direct, and Google Scholar. From an initial collection of 190 records, only 7 studies met the eligibility standards after screening. The malignant transformation rate observed across these selected publications spanned from 3.72% to 38.15%. Among the identified risk factors, habitual betel quid consumption emerged most prominently in association with cancer progression. Interestingly, the rates identified in this review exceed the commonly cited transformation statistics, signaling a need for heightened clinical alertness. Routine biopsy is crucial when managing such lesions to exclude underlying dysplastic or malignant alterations. A notable lack of long-term follow-up studies—particularly among Indian populations—was also observed, indicating a pressing gap in existing research and a need for more extensive research in this field.

Keywords: Risk factors, Oral potentially malignant disorder, Malignant transformation rate, Oral submucous fibrosis, Follow-up

Introduction

Oral submucous fibrosis (OSMF), initially reported in 1952 [1], is acknowledged as a chronic and progressively worsening precancerous disorder that affects both the oral cavity and pharynx. The primary agent implicated in its etiology is arecoline, a component of the areca nut [2]. Clinically, OSMF manifests through mucosal pallor, a persistent burning sensation, thickening of the oral lining, and increasing fibrosis, ultimately resulting in trismus, which compromises speech and deglutition [3]. Globally, areca nut chewing ranks as the fourth most widespread substance use habit [4], commonly consumed in blends that may include betel quid, tobacco, and slaked lime. The usage patterns show significant variation across different regions within India and other countries [5].

Various studies across distinct populations have attempted to quantify the malignant transformation rate (MTR) of OSMF. While one investigation recorded a 7.6% transformation rate after a 17-year follow-up, another Indian study reported a considerably lower MTR of 2.6% [5]. According to IARC, the highest observed MTR in India remains at 7.6% [6]. Evaluating the malignant potential of Oral potentially malignant

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disorders such as OSMF is vital for clinicians to ensure early diagnosis and timely management, which can markedly enhance patient outcomes. This review, therefore, seeks to consolidate findings on the malignant transformation rate of OSMF and identify the associated risk factors.

Materials and Methods

Prior approval was secured from the institutional scientific review board at Saveetha Dental College, under the Saveetha Institute of Medical and Technical Sciences, Chennai. A literature search targeting the period from 2014 to 2019 was carried out across multiple databases including PubMed, Cochrane Library, Science Direct, and Google Scholar. The inclusion criteria focused on observational follow-up studies specifically examining OSMF cases for Malignant transformation, as well as studies on oral potentially malignant disorders encompassing OSMF with reported MTR values. Studies were excluded if they followed an interventional design, lacked follow-up data on MTR in OSMF, or were centered on other types of oral potentially malignant disorders without specific reference to OSMF.

Results and Discussion

All selected studies were analyzed to determine the overall malignant transformation rate as well as the annual transformation figures (ATR) (**Table 1**). Among the cumulative total of 5,043 documented OSMF lesions/cases across the seven studies reviewed, 706 instances progressed to malignancy. These studies also examined correlations between malignant transformation and variables such as the type, duration, and frequency of harmful habits (**Table 2**). The methodological quality of the studies was evaluated using the BSA Medical Sociology Group's assessment tool for cross-sectional research.

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 and 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	2013	8.9%	NA	NA	NA	NA
	2. Ever cigarette smoking	2138	8.4%				
	3. Ever alcohol drinking	1539	10.0%				
	4. Betel nut chewing and cigarette smoking	572	NA				
		113	NA				
	5. Betel nut chewing and alcohol drinking	110	NA				
		1316	NA				

	6. Cigarette smoking and alcohol drinking 7. Having three habits						
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 3. Betel quid only 4. Betel quid and smoking 5. Betel quid and alcohol 6. Betel, smoking, and 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	1. Alcohol drinking 2. Betel quid chewing 3. Cigarette smoking	728 879 857	NA*	NA	NA	NA	NA

This systematic review sought to compile and analyze data from observational studies to determine the malignant transformation rate (MTR) of oral submucous fibrosis (OSMF). Although a widely cited hospital-based investigation from Taiwan previously reported an MTR range of 7–13% [7], our review uncovered a considerably broader spectrum of transformation rates, spanning from 3.72% to as high as 38.15%, based on findings from seven studies conducted in varied demographic settings. Among these, the study by Wang *et al.* [8] documented the lowest MTR at 3.72%, followed sequentially by Jayasinghe *et al.* [9] at 5.90%, Chuang *et al.* [10] at 7.69%, Yang *et al.* [11] at 9.13%, Nayak *et al.* [12] at 10.34%, and Chien–Yang Yeh *et al.* [13] at 11.0%. The most extreme rate was recorded by Mohiuddin *et al*. [14], who reported a striking MTR of 38.15% in their multicentric analysis involving both private and public tertiary healthcare centers in Pakistan. Their study monitored 765 patients diagnosed with OSMF, of whom 472 progressed to oral squamous cell carcinoma (OSCC) during a mean follow-up period of eight years. The follow-up durations in the remaining studies ranged between 3.6 and 10 years.

The annual transformation rate (ATR) offers a more dynamic view of the progression timeline and serves as an important tool for oral medicine practitioners when evaluating patient prognosis [15]. Within the reviewed literature, only the investigation conducted by Chuang *et al.* [10] explicitly reported an ATR, noting 8.6 malignancies per 1000 person-years; the rest limited their findings to cumulative MTR values.

The longstanding association of OSMF with areca nut and betel quid chewing has been well-established, particularly in the context of increasing oral cancer incidence among affected individuals [16–18]. Numerous studies, including those in this review, underscore the carcinogenic potential of betel quid when combined with tobacco, often displaying a dose-response relationship [19]. Jayasinghe *et al.* [9] categorized participants according to their primary chewing habit—either areca nut or betel quid—and further subdivided betel quid users based on coexisting habits such as tobacco smoking or alcohol consumption. Interestingly, the highest MTR was noted among those who chewed only betel quid, while individuals who exclusively consumed areca nut did not experience malignant

progression. In contrast, Mohiuddin *et al*. [14] excluded alcohol and cigarette use from their classification and instead categorized patients based on five habit types: areca nut alone, betel quid with tobacco, betel quid without tobacco, naswar, and those without any known risk habits. Their findings showed the highest MTR in the group consuming betel quid with tobacco, followed by the areca nut-only group.

A more nuanced classification of Risk factors was demonstrated in the study by Chuang *et al.* [10], where patients were grouped according to single and combined habits. Although this design offered valuable insight into habit interactions, MTRs for the groups with multiple concurrent habits were not individually specified. The role of habit frequency and duration in influencing MTR is well-recognized; however, most studies did not document these variables. Only Jayasinghe *et al*. [9] incorporated this dimension, stratifying betel quid users based on the daily number of quids consumed and the duration of usage, ranging from less than a year to over 25 years. Their results, however, indicated no statistically significant variation in MTR relative to the frequency of quid consumption.

Conclusion

The range of malignant transformation rate (MTR) for Oral submucous fibrosis (OSMF), as identified across the seven observational studies included in this review, extended from 3.72% to 38.15%. Among the contributing Risk factors, betel quid chewing emerged as the most prominent habit associated with an elevated risk of progression to malignancy.

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