Malignant transformation of oral submucous fibrosis: a systematic review and meta-analysis

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Running title: Malignant transformation of OSF

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Abstract

Objectives: This systematic review and meta-analysis aimed to determine the proportion of cases who develop oral carcinomas in patients diagnosed with oral submucous fibrosis (OSF) in reported longitudinal studies. We also aimed to evaluate the demographic and clinicopathological factors contributing to the progression of OSF to cancer.

Methods: Individual search strategies were applied for the following bibliographic databases: MEDLINE by PubMed, Scopus, Embase, Web of Science, and Grey literature databases until August 30, 2020. Methodological assessment of the risk of bias of the included studies was undertaken using the modified Newcastle-Ottawa scale. Meta-analyses were conducted using a random-effects (DerSimonian and Liard) method to calculate the pooled proportion of the MT in OSF patients.

Results: Out of 585 records screened, a total of 9 observational studies were included with a total number of patients of 6,337 cases; of these, 292 OSF cases developed carcinoma. The pooled proportion of the malignant transformation was 4.2% (95% CI: 2.7%-5.6%) with an annual transformation rate of 0.73%. Subgroup analysis revealed that the pooled MT proportion was significantly higher among population-based studies in comparison to hospital-based ones ($p < 0.005$). Most of the studies showed high risk of bias. In several studies, there was a lack of information about the demographic and clinicopathological characteristics of OSF patients and associated risk indicators; this insufficiency in details hindered the ability to conduct further subgroup analyses.

Conclusions: Despite the poorly reported and the limited number of studies, our analysis confirms that close to 4% of patients diagnosed with OSF may develop oral cancer. Cases with OED had higher potential for transformation.
1. Introduction

Oral submucous fibrosis (OSF) is a chronic, insidious disease characterized by progressive submucosal fibrosis of the oral cavity and the oropharynx (Warnakulasuriya, Tillakaratne, & Kerr, 2017). OSF leads to stiffness in oral mucosa, fibrous banding, limitation in mouth opening, and some cases could be associated with the development of oral squamous cell carcinoma (OSCC) (Cox & Walker, 1996; Warnakulasuriya, 2018). OSF frequently affects the buccal mucosa, and it may also affect other sites including lips, soft palate, pharynx, esophagus, and the larynx (Kerr et al., 2011; Tilakaratne, Ekanayaka, & Warnakulasuriya, 2016). This disorder is more commonly reported in India; whereas, cases and case-series were also described in other locations, such as Pakistan, Sri Lanka, Nepal, Taiwan, Southern China, Thailand, Vietnam, Myanmar, Papua New Guinea, Islands in Micronesia, and also in Durban, South Africa (Rao et al., 2020). Areca nut/betel quid chewing habits are strongly associated with the development of OSF (IARC, 2004). Studies in India, Taiwan, Pakistan, and Sri Lanka found a significant dose-response relationship between areca nut and OSF development, the odds ration among these studies ranged between 1.2 (95% CI: 0.7 to 2.04) to 246 (95% CI: 47 to 1278) (Tilakaratne et al., 2016).

Oral submucous fibrosis has been classified using various clinical, histological, and functional schemes (Ranganathan & Mishra, 2006), and use of different classification systems caused confusion in the literature as to the essential clinical criteria to diagnose OSF (More et al., 2012; Arakeri et al., 2018). Early clinical signs of OSF include blanching of the oral mucosa, leathery mucosal texture, loss of tongue papillae, and burning sensation to spicy food (Zain et al., 1999; Warnakulasuriya et al., 2017). During development, OSF progresses to form bands of fibrosis leading to restricted movement or opening depending on the location of fibrous bands. Advanced cases may present with marbling of mucosa, depigmentation, hypomobility of tongue and soft palate, xerostomia, sunken cheeks, and significant morbidities (More & Rao, 2019). Histological changes of OSF include epithelial alterations of atrophy, hyper-parakeratosis or -orthokeratosis, and a variable degree of fibrosis in the connective tissue. Features of oral epithelial dysplasia can also be observed (Ray, Ranganathan, & Chattopadhyay, 2016; Siriwardena, Jayawardena, Senarath, & Tilakaratne, 2018). The WHO Collaborating Center for Oral Cancer has classified OSF as an oral potentially malignant disorder (OPMD) (Warnakulasuriya, Johnson, & van der Waal, 2007), and this is re-affirmed in their recent report (Warnakulasuriya et al., 2020). First report
of malignant transformation of OSF goes back to 1956 (Paymaster, 1956). Since then, several studies reported variable rates of progression to cancer in patients diagnosed with OSF ranging from 5 to 13% (Ekanayaka & Tilakaratne, 2016; Iocca et al., 2020; Phulari & Dave, 2020). This wide range probably relates to the variabilities among the reported studies, such as patients’ setting, hospital or population base, and social behaviors, in addition to the length of follow up. Most recently, Iocca et al. reported that the overall global estimate of the malignant transformation (MT) of 5.2% (99% CI: 2.9%-8.0%) for the OSF based on four included studies (Iocca et al., 2020). This systematic review and meta-analysis is aimed to determine the overall malignant transformation proportion of OSF in longitudinal studies. Our secondary aim was to examine the demographic and clinicopathological factors contributing to progression of OSF to cancer.

2. Materials and Methods
2.1 Protocol and registration
This systematic review and meta-analysis was registered as a protocol in the International Prospective Register of Systematic Reviews (PROSPERO) platform (CRD42020160187), and the reporting was carried out following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

2.2 Focused questions
This review was designed to answer the following questions: (1) what is the global proportion of malignant transformation in OSF? and (2) what are the clinico-pathological factors contributing to malignant transformation of OSF cases?

2.3 Eligibility criteria
Participants: Subjects diagnosed with clinical and/or histopathological diagnosis of oral submucous fibrosis were included. We did not impose any minimum clinical criteria for the diagnosis of OSF in primary studies. However, the following groups of patients were excluded: (1) patients with the diagnosis of other oral potentially malignant disorders, (2) patients with the diagnosis of OSCC at the onset of the study, and (3) patients diagnosed with other white patches.

Primary outcome: The global proportion of OSF patients with proven history of OSCC.
Secondary outcome: Association between malignant transformation of OSF and geographic region, anatomical sites, age, gender, risk indicators (smoking, alcohol consumption, and betel quid/areca nut chewing), malnutrition (e.g., anemias), period of follow-up, treatment
modality, presence of epithelial dysplasia, morphological features such as epithelial atrophy and vascularity of the corium, and any biomarkers studied, if these data were reported.

**Types of studies:** Observational studies, with a minimal follow-up period of six months, published in the English language from 1945 until 30 August 2020 were included. Letters to the editor, case reports, conference abstracts, clinical trials, and systemic reviews and meta-analysis were excluded.

### 2.4 Search strategy and Data extraction

The following databases: MEDLINE by PubMed, Scopus, Embase, and Web of Science, in addition to grey literature databases were searched using a developed search strategy until August 30, 2020 (Supplementary Table 1). In addition, manual search for the past 10 years of Journal of Oral Pathology and Medicine, Oral Diseases, Oral Oncology, and BMC Oral Health was attempted to identify any relevant studies. The reference list from the included studies was also screened for further inclusion in this study.

The titles and abstracts of the references retrieved during the searches were firstly screened for relevance by two reviewers (OK, FWM). Secondly, the reviewers assessed the full-text versions of the articles identified as being potentially eligible for inclusion against the inclusion/exclusion criteria. Those meeting the eligibility criteria were selected for inclusion. If essential data for the review were missing or unclear, an attempt was made to contact the corresponding author of the study to resolve or clarify the problem. Any discrepancies between the reviewers were resolved by discussion and consensus.

For studies meeting inclusion criteria, the two reviewers collected the following details from each study: authors, year of publication, type of study, number of cases, sex and age of the patient, clinical presentation, type and grade of the lesion, follow-up, location of the lesion, presence of epithelial dysplasia, presence of known cancer risk factors, rate of malignant transformation, time until the malignant onset, type of carcinoma, treatment modality, and co-morbidities, if reported.

### 2.5 Risk of bias of individual studies

Newcastle-Ottawa scale for risk of bias assessment was used in this study to assess the quality of the included studies. However, this scale was modified from the original to be compatible with the aims of this study (Aghbari et al., 2017; Fitzpatrick, Hirsch, & Gordon, 2014). Items were categorized into two groups and each item was worth one point. The maximum allocated was six points (Supplementary Table 2). The quality of the studies was classified according to the final score into: poor (score 0-2), moderate (score 3-4), and high (score 5-6).
2.6 Data analysis
Meta-analyses were conducted using a random-effects (DerSimonian and Liard) method to calculate the pooled proportion of the MT in OSF patients. A 95% confidence interval was chosen for analysis. Cochran’s Q test was used to assess the heterogeneity among studies. The level of heterogeneity was identified according to Higgins \(I^2\) statistic as 25%, 50%, and 75% indicating low, moderate, and high, respectively (Higgins, Thompson, Deeks, & Altman, 2003). All analysis was performed using OpenMeta software (Boston, USA) and Review Manager 5.3 (Copenhagen, Denmark).

3. Results
3.1 Results of database search
Five hundred and eighty-five records were screened by abstract reading, after duplicate removal (Figure 1). Of these, only 16 studies underwent full-text assessment. Seven studies were deemed to be ineligible for inclusion and the reasons for exclusion are shown in supplementary Table 3 (Hegde., Anuradha., & Asha., 2015; McGurk & Craig, 1984; Mohiuddin, Fatima, Hosein, & Fatima, 2016; Pindborg et al., 1984; Rangaswamy, Chikkalingaiah, Sanjeevarayappa, & Govindraju, 2019; T. Wang et al., 2018; Zhou et al., 2008). Among the nine included studies, five studies were from Taiwan (Chiang et al., 2020; Chuang et al., 2018; Hsue et al., 2007; Y. Wang et al., 2014; Yang et al., 2017), followed by India with three studies (Chourasia, Borle, & Vastani, 2015; Hazarey, Erlewad, Mundhe, & Ughade, 2007; Murti et al., 1985), while there was only one study reported from China (Tang, Jian, Gao, Ling, & Zhang, 1997). A summary of the included studies characteristics and results is available in Table 1.

3.2 General description of the included studies
Out of the nine studies, five studies were designed to include only OSF in their study design (Chourasia et al., 2015; Hazarey et al., 2007; Murti et al., 1985; Tang et al., 1997; Yang et al., 2017), and four studies were designed to include other OPMDs and reported separated data for OSF (Chiang et al., 2020; Chuang et al., 2018; Hsue et al., 2007; Y. Wang et al., 2014). Interestingly, there was lack of inconsistency in reporting the diagnostic criteria of OSF. Only three included studies provided clear description of their used criteria. Yang et al., mentioned that the code that they used for OSF diagnosis was ICD-9-CM code: 528.8 (Yang et al., 2017). However, Hazarey et al. (2007) provided more details about the clinical and histopathological criteria of OSF diagnosis. Their clinical criteria were the presence of palpable fibrous bands or stiffness of a large area of oral mucosa and the presence of...
blanching of the mucosa that did not resolve after stopping smoking or other habits that could cause this kind of blanching (Hazarey et al., 2007). Surgical biopsies were taken from nearly 30% of the included OSF patients for histopathological assessment that was determined using the following criteria: 1) juxtaepithelial fibrosis with atrophy or hyperplasia of the overlying epithelium, 2) keratinizing metaplasia and accumulation of hyalinised collagen beneath the basement membrane with a progressive loss of vascularity, and 3) a viable chronic inflammatory cells infiltration in the lamina propria (Hazarey et al., 2007). Lastly, Murti et al., stated that the included OSF cases were diagnosed according to the standard criteria of Mehta (1971). Interestingly, only Yang et al., reported that the use of ICD-9-CM codes: 140-149 for the diagnosis of oral cancer (Yang et al., 2017). While two studies used cancer registry databases to report the malignant transformation cases (Chuang et al., 2018; Hsue et al., 2007). However, the other included primary studies did not state the criteria of oral cancer diagnosis in their reports.

The total number of OSF patients included in these studies was 6,337, more than 75% of them were from the Taiwanese studies (Table 1). Regarding the designs of the studies, five studies were retrospective and four were prospective with the mean follow-up periods 6.5 years (standard deviation 2.7) (Chiang et al., 2020; Chuang et al., 2018; Hsue et al., 2007; Murti et al., 1985). One study excluded females from the sample (Chuang et al., 2018) and three did not report information regarding gender distribution (Chiang et al., 2020; Hsue et al., 2007; Murti et al., 1985). Among the remaining five studies, the total proportion of male in the combined sample was 86% (ranged from 75% to 92%).

Two studies stated the presence or absence of epithelial dysplasia among their OSF patients’ cohorts (Hsue et al., 2007; Y. Wang et al., 2014), and one study reported the number of OSF cases associated with oral leukoplakia (Yang et al., 2017).

3.3 Risk of bias of individual studies

Based on the modified NOS scale, the quality of two studies was moderate while the others was poor as shown in the supplementary Table 4. Only four studies reported the mean age of their patient’s cohort (Chourasia et al., 2015; Hazarey et al., 2007; Y. Wang et al., 2014; Yang et al., 2017). Moreover, only one study provided individual details on patients who underwent MT separately (Murti et al., 1985).

3.4 The proportion of MT among OSF cases

Out of the included 6,337 cases, 292 cases progressed to carcinoma with an overall pooled proportion of OSCC of 4.2% [95% CI: 2.7%-5.6%] (Figure 2) and the annual transformation
rate was 0.73%. Only one study reported the gender of patients who underwent MT (Table 1) (Murti et al., 1985). Therefore, a meta-analysis to assess the influence of gender in the MT of OSF cases was not possible to be performed. A high degree of heterogeneity among studies was found according to the Higgins cutoff point ($I^2=86.37, P<0.001$) (Higgins et al., 2003). The histological subtypes of carcinoma that arose in OSF patients were stated in two studies. Hazarey et al. reported that out of 33 carcinoma cases there were 28 OSCC and five verrucous carcinomas (Hazarey et al., 2007), whilst Chourasia et al. revealed that all five carcinoma cases were diagnosed as OSCC (Chourasia et al., 2015). Our results revealed a significant association between the presence of epithelial dysplasia or oral leukoplakia and the MT proportion among OSF patients, $p < 0.005$ (Figure 3). Forty out of 414 OSF patients with oral leukoplakia or epithelial dysplasia (9.7%) exhibited MT compared to 78 out of 1,963 of OSF patients without epithelial dysplasia or oral leukoplakia (4%), $p < 0.005$.

3.5 Subgroup meta-analysis

Subgroup analysis revealed that the pooled proportion of MT was higher in Taiwanese compared to Indians, 4.9% and 3.5%, respectively, however, the association was not significant ($p = 0.677$) (Figure 4 A). According to the sample’s setting, our results revealed that the MT proportion among the population-based studies was higher than the MT proportion among the hospital-based ones, 5.3% and 3.3%, respectively, ($p < 0.005$) (Figure 4 B). Finally, there was no significant association between the quality level of the included studies and the MT proportion as shown in Figure 4 C ($p =0.681$).

4. Discussion

The results of this meta-analysis report a global MT proportion of OSF 4.6% with an annual rate of 0.73%. Iocca et al. recently investigated the malignant transformation rate of oral potentially malignant disorders including OSF. In their sub-analysis, that consisted of 4 OSF studies, they showed an overall proportion of OSF cases progressed to cancer (5.2%) and the annual transformation rate was 0.98% (Iocca et al., 2020). Interestingly, it seems that malignant transformation of OSF has received much less attention by the scientific community, compared to other OPMDs specifically leukoplakia and oral lichen planus (Iocca et al., 2020). Our searches also yielded only a small number of publications on the OSF topic. This can be attributed to the fact that this condition is often confined to specific geographic regions in the world, in particular, South and South East Asia. Limited available resources in low and middle income countries and lack of attention to
for follow up studies in this region may influence the limited amount of quality studies on this specific topic. Nevertheless, this pattern of prevalence limited to designated geographic regions does not mean that this condition is rare. On contrary, OSF is widely prevalent (global prevalence estimated in 4.96%; 95% CI = 2.28-8.62%) (Mello et al., 2018) as it is strongly linked to the habits of chewing betel quid/areca nut, and these habits are regularly practiced by about 10% to 20% of the world’s population (IARC 2012; Gupta & Warnakulasuriya, 2002). This is truly reflected in our findings as eight out of nine studies included in this systematic review were carried out in India and Taiwan (Chiang et al., 2020; Chourasia et al., 2015; Chuang et al., 2018; Hazarey et al., 2007; Hsue et al., 2007; Murti et al., 1985; Y. Wang et al., 2014; Yang et al., 2017).

As stated earlier, the available demographic information was very limited which restricts the ability to run more detailed analysis of OSF-MT associated risk indicators. Although five studies reported the gender of their cohorts (Chourasia et al., 2015; Hazarey et al., 2007; Tang et al., 1997; Y. Wang et al., 2014; Yang et al., 2017), only one study reported the gender of OSF patients who underwent MT (Y. Wang et al., 2014). Poorly reported primary studies noted in this systematic review raises the importance of following reporting guidelines such as Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observation studies (von Elm et al., 2007).

Our results revealed that the MT proportion was significantly higher among the population-based studies compared to the hospital-based studies. However, this can be attributed to many factors other than the OSF by itself. Firstly, the number of the included Taiwanese patients in the population-based studies was more than 88% compared to less than 12% from India and China, which could be a source of bias. Especially when taking into consideration that the crude incidence rate of oral cancer in Taiwan is the highest in the world according to the Cancer Registry Annual Report of Taiwan in 2016 (32.46 per 100,000 persons) (Hung et al., 2020) in comparison to 8.9 per 100,000 persons and 2.00 per 100,000 persons in India and China, respectively (Ferlay et al., 2018). Noteworthy, our results indicated that there was a significant association between the presence of epithelial dysplasia and the MT of OSF \( (p < 0.005) \). This finding is expected as there is a cumulative evidence to support that the presence of epithelial dysplasia increases cancer risk, in most types of OPMDS (Speight, Khurram, & Kujan, 2018) and in particular in OSF (Jayasooriya, Jayasinghe, & Tilakaratne, 2011; Ray, Ranganathan, & Chattopadhyay, 2016; Ranganathan & Loganathan, 2019). This raises the importance of assessing the role of epithelial dysplasia when reporting the MT risk of OSF in future studies and calibration of oral pathologists to grade dysplasia (Ranganathan et al.,

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2020). Reporting such information would be essential to understand those who may carry higher risk of MT. The primary studies included did not report on other risk indicators, like smoking and alcohol consumption habits. Thus, we were unable to carry out additional analyses to explore the role of different variables in the MT of OSF.

The factors associated with OSF development are well documented (IARC, 2004; Tilakaratne et al., 2016). It is well-established that chewing areca nut (*Areca catechu*) is the major causative factor of OSF (IARC, 2004). Areca nut increases cells’ oxidative stress that leads to DNA damage (Yadav et al., 2020). The disruption of cyclin-dependent kinases has also postulated in the oral carcinogenesis (Kujan et al., 2019). Nonetheless, few studies did not report the details of areca nut chewing habits of patients in their follow up studies (Hsue et al., 2007; Yang et al., 2017). Other studies reported that more than 90% of OSF patients were betel-quid chewers (Chourasia et al., 2015; Tang et al., 1997; Y. Wang et al., 2014).

Moreover, Hazarey et al. recruited 1000 OSF patients and they only found that 1.7% of the patients did not reveal a history of chewing habits (Hazarey et al., 2007). Noteworthy, genetic polymorphisms (Warnakulasuriya et al., 2017), micronutrient deficiencies (Maher, Aga, Johnson, Sankaranarayanan, & Warnakulasuriya, 1997) and immunological predispositions are additional contributing risk factors for OSF (among areca chewers) that should be considered during the study of this condition (Rajalalitha & Vali, 2005). However, none of the included studies investigated these factors in relation to MT in OSF patients.

Although areca nut is strongly linked with oral cancer (IARC, 2004), the underlying mechanism that explains areca nut carcinogenesis is still unclear (Ekanayaka & Tilakaratne, 2016; Hernandez et al., 2017). Experimental studies have demonstrated that areca nut alkaloids including arecoline have induced chromosomal aberrations, repressed DNA repair pathway, and activated DNA damage response in human keratinocytes (Tsai et al., 2008). The understanding of such mechanisms will help in developing targeted therapies that could block molecular pathways involved in carcinogenesis (Dione et al., 2015; Kujan et al., 2019; Kujan et al., 2020). Also, the use of a comprehensive staging system employing all clinical, histopathological, and functional data would help in the consistent reporting of OSF. Kerr et al (2011) in their proposed staging system for OSF considered the presence of leukoplakia or dysplasia in OSF to be grouped as Stage 4 disease. This is borne by the findings in this SR as cases with OED had higher potential for transformation. We noted the included studies in this systematic review utilized different classification systems for the diagnosis and grading of OSF. Three included studies stated various clinicopathological criteria for case selection but there was no uniformity in these case inclusion criteria. (Hazarey, Erlewad, Mundhe, &
Ughade, 2007; Murti et al., 1985; Yang et al., 2017). The lack of consistency in reporting the clinical demographics and risk factors is a limitation of the extracted data from the included studies. We believe that the lack of consistent diagnostic criteria and classification system of OSF adds more confusion to the existing literature. Future studies would benefit by using criteria proposed proposed by Kerr et al. (2011) (Kerr et al., 2011). Furthermore, the included studies did not report the demographics and clinicopathologic features of OSCC occurring with a previous OSF diagnosis. Thus, it is still undetermined if OSCC occurring with and without a previous OSF would share similar prognostic and predictive characteristics (Chaturvedi et al., 2013). As revealed by this systematic review, there is a significant lack of information in the published literature on the natural history of OSF and future studies are warranted.

Generally, studies with positive results are considered more "valuable" and have higher chances of being published and cited by other studies. Still, the publication of negative results is important to avoid misinformation and waste of resources in academia (Mlinarić, Horvat, & Šupak Smolčić, 2017; Nair, 2019). Aiming to investigate the presence of a possible publication bias, it is recommended that authors of systematic reviews perform formal analyses, such as funnel plots. However, there are several possible sources of asymmetry in funnel plots and, in analyses with less than ten studies with high heterogeneity the power of the test is usually too low to distinguish chance from real asymmetry (Lau et al., 2006; Sterne et al., 2011). Therefore, to avoid misleading results, we did not consider appropriate to perform statistical analyses regarding publication bias (e.g., Funnel Plots and Egger's test) in this systematic review. We alert for a possible publication bias, which needs to be investigated in further systematic reviews when more studies about OSF MT are available.

We are conscious that this study may have several limitations. The inclusion of only studies published in English language might lead to the missing of some publications available in other languages. The diversity on the diagnostic and classification criteria of OSF in the included studies could be regarded another limitation. Due to the lack of some basic information regarding the included cohorts, we were unable to undertake any additional subgroup analyses according to their risk habits, underlying systemic conditions, and anatomical sites susceptible to MT. Finally, we report a high level of heterogeneity, which may affect the reliability of the outcomes of some included studies.

5. Conclusions
There are limited details of the characteristics of OSF patients who underwent malignant transformation and the associated risk indicators. Despite the poorly reported studies, our analysis confirms that OSF is a condition associated with a malignant transformation pooled proportion of 4.2% (95% CI: 2.7%-5.6%). Nevertheless, further well-designed, longitudinal studies investigating the malignant transformation in OSF patients are required.

Conflict of interests
Authors declare no conflict of interest.

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Ethics considerations
This is a systematic review/meta-analysis and no ethical approval was required.

Funding
No funding was received.
Table 1: A summary of the included studies and the number of malignant transformed cases

<table>
<thead>
<tr>
<th>Authors/Year</th>
<th>Country</th>
<th>Design</th>
<th>Total (n)</th>
<th>Mean age (years)</th>
<th>MT (n)</th>
<th>Overall MT proportion</th>
<th>Annual MT rate</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiang et al. 2020</td>
<td>Taiwan</td>
<td>P Hospital-based</td>
<td>87</td>
<td>NR</td>
<td>4</td>
<td>4.6%</td>
<td>0.69%</td>
<td>6.7</td>
</tr>
<tr>
<td>Chuang et al. 2018</td>
<td>Taiwan</td>
<td>P National-based</td>
<td>2333</td>
<td>M 2333, F excluded</td>
<td>NR</td>
<td>114</td>
<td>4.8%</td>
<td>0.86%</td>
</tr>
<tr>
<td>Yang et al. 2017</td>
<td>Taiwan</td>
<td>R National-based</td>
<td>778</td>
<td>M 678, F 100</td>
<td>41.8 ±11.7</td>
<td>71</td>
<td>9.1%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Chourasia et al. 2015</td>
<td>India</td>
<td>R Hospital-based</td>
<td>119</td>
<td>M 88, F 31</td>
<td>33.80 M 30.70, F 31.51</td>
<td>5</td>
<td>4.2%</td>
<td>-</td>
</tr>
<tr>
<td>Wang et al. 2014</td>
<td>Taiwan</td>
<td>R Hospital-based</td>
<td>1,180</td>
<td>M 1,091, F 89</td>
<td>44.69 ± 12.43</td>
<td>46</td>
<td>3.9%</td>
<td>-</td>
</tr>
<tr>
<td>Hazarey et al. 2007</td>
<td>India</td>
<td>R Hospital-based</td>
<td>1000</td>
<td>M 830, F 170</td>
<td>M 27.60 ± 9.58, F 34.78 ± 12.21</td>
<td>33</td>
<td>3.3%</td>
<td>0.66%</td>
</tr>
<tr>
<td>Hsue et al. 2007</td>
<td>Taiwan</td>
<td>P Hospital-based</td>
<td>439</td>
<td>NR</td>
<td>10</td>
<td>2.3%</td>
<td>0.55%</td>
<td>3.6</td>
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<tr>
<td>Tang et al. 1997</td>
<td>China</td>
<td>R Population-based</td>
<td>335</td>
<td>M 252, F 83</td>
<td>NR</td>
<td>4</td>
<td>1.2%</td>
<td>-</td>
</tr>
<tr>
<td>Murti et al.</td>
<td>India</td>
<td>P</td>
<td>66</td>
<td>NR</td>
<td>5</td>
<td>7.6%</td>
<td>0.76%</td>
<td>10</td>
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<tr>
<td>1985</td>
<td>Population-based</td>
<td>M 0, F 5</td>
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<tr>
<td>Total</td>
<td>6,114</td>
<td>281</td>
<td>4.6%</td>
<td>0.73%</td>
<td>6.25</td>
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</table>

MT: malignant transformation, P: prospective, R: retrospective, M: male, F: female, n: number; NR: Not reported

Figure 1: PRISMA flow chart of the screened and included studies

Figure 2: Forest plot of the MT proportion among the OSF cases and the level of heterogeneity

Figure 3: Forest plot for the role of epithelial dysplasia or oral leukoplakia in the MT of OSF cases

Figure 4: Forest plots for the association between the MT of OSF cases according to the country (A), patient’s setting (B), and the risk of bias level (C)
References


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Nair, A. S. (2019). Publication bias-Importance of studies with negative results!. *Indian J Anaesth, 63*(6), 505.


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Records identified through database searching (n = 1,697)

Records after duplicates removed (n = 585)

Records screened (n = 585)

Records excluded (n = 569)

Full-text articles assessed for eligibility (n = 16)

Full-text articles excluded, with reasons (n = 7)

Studies included in analysis (n = 9)

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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>M.H. Fixed, 95% CI</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hue 2007</td>
<td>2</td>
<td>57</td>
<td>8</td>
<td>4.9%</td>
<td>2.81 [0.68, 10.77]</td>
</tr>
<tr>
<td>Wang 2014</td>
<td>9</td>
<td>186</td>
<td>37</td>
<td>37.2%</td>
<td>1.32 [0.62, 2.77]</td>
</tr>
<tr>
<td>Yang 2017</td>
<td>28</td>
<td>191</td>
<td>43</td>
<td>58.3%</td>
<td>2.33 [1.40, 3.85]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>454</td>
<td>1983</td>
<td>100.0%</td>
<td>1.87 [1.32, 2.64]</td>
</tr>
</tbody>
</table>

Heterogeneity: Q(2) = 1.73, df = 2 (P = 0.42); I² = 0%
Test for overall effect Z = 1.33 (P = 0.090)
<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% CI:</th>
<th>Event/TIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng</td>
<td>0.446 (0.002, 0.800)</td>
<td>4/97</td>
</tr>
<tr>
<td>Chuang</td>
<td>0.449 (0.041, 0.858)</td>
<td>11/233</td>
</tr>
<tr>
<td>Yang</td>
<td>0.691 (0.070, 0.331)</td>
<td>11/778</td>
</tr>
<tr>
<td>Wang</td>
<td>0.639 (0.0004, 0.900)</td>
<td>64/1180</td>
</tr>
<tr>
<td>Hao</td>
<td>0.623 (0.003, 0.977)</td>
<td>10/439</td>
</tr>
<tr>
<td><strong>Subgroup: Taiwan (P²=0.8778, P=0.000)</strong></td>
<td><strong>0.143 (0.033, 0.967)</strong></td>
<td><strong>245/421</strong></td>
</tr>
<tr>
<td>Choue</td>
<td>0.142 (0.004, 0.879)</td>
<td>5/119</td>
</tr>
<tr>
<td>Harayu</td>
<td>0.135 (0.022, 0.904)</td>
<td>13/1090</td>
</tr>
<tr>
<td>Muni</td>
<td>0.776 (0.011, 0.960)</td>
<td>5/66</td>
</tr>
<tr>
<td><strong>Subgroup: India (P²=0.000)</strong></td>
<td><strong>0.395 (0.028, 0.895)</strong></td>
<td><strong>63/1335</strong></td>
</tr>
<tr>
<td>Tang</td>
<td>0.632 (0.000, 0.826)</td>
<td>4/235</td>
</tr>
<tr>
<td><strong>Subgroup: China (P²=NA, P=NA)</strong></td>
<td><strong>0.431 (0.009, 0.856)</strong></td>
<td><strong>212/5337</strong></td>
</tr>
<tr>
<td><strong>Overall (P²=0.8877, P=0.000)</strong></td>
<td><strong>0.442 (0.027, 0.856)</strong></td>
<td><strong>212/5337</strong></td>
</tr>
<tr>
<td>Status</td>
<td>Estimate</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Chang</td>
<td>0.944</td>
<td>(0.902, 0.986)</td>
</tr>
<tr>
<td>Chang's</td>
<td>0.962</td>
<td>(0.906, 0.930)</td>
</tr>
<tr>
<td>Chang's</td>
<td>0.939</td>
<td>(0.986, 0.995)</td>
</tr>
<tr>
<td>Tung</td>
<td>0.953</td>
<td>(0.932, 0.966)</td>
</tr>
<tr>
<td>Year</td>
<td>0.923</td>
<td>(0.900, 0.937)</td>
</tr>
<tr>
<td>Subgroup hospital-based (129 of 7, P=0.000)</td>
<td>0.933</td>
<td>(0.927, 0.939)</td>
</tr>
<tr>
<td>Chang</td>
<td>0.985</td>
<td>(0.964, 0.998)</td>
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<tr>
<td>Tung</td>
<td>0.993</td>
<td>(0.973, 0.999)</td>
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<tr>
<td>Tung's</td>
<td>0.982</td>
<td>(0.990, 0.996)</td>
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<tr>
<td>Subgroup population-based (129 of 44, P=0.000)</td>
<td>0.983</td>
<td>(0.922, 0.987)</td>
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<tr>
<td>Overall (129 of 54, P=0.000)</td>
<td>0.942</td>
<td>(0.925, 0.959)</td>
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<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>EVT/Ttr</th>
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</thead>
<tbody>
<tr>
<td>Chang</td>
<td>0.046 (0.302, 0.098)</td>
<td>4/87</td>
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<tr>
<td>Chang Subgroup 3 (P&gt;0.5 %, P&lt;0.001)</td>
<td>0.049 (0.540, 0.505)</td>
<td>124/2453</td>
</tr>
<tr>
<td>Yang</td>
<td>0.033 (0.071, 0.131)</td>
<td>72/779</td>
</tr>
<tr>
<td>Hazey Subgroup 6 (P&gt;0.95 %, P&lt;0.001)</td>
<td>0.043 (0.594, 0.139)</td>
<td>104/2779</td>
</tr>
<tr>
<td>Draweesa</td>
<td>0.042 (0.056, 0.678)</td>
<td>5/129</td>
</tr>
<tr>
<td>Tang</td>
<td>0.013 (0.000, 0.034)</td>
<td>4/335</td>
</tr>
<tr>
<td>Subgroup 4 (P&lt;0.10 %, P&lt;0.01)</td>
<td>0.022 (-0.006, 0.059)</td>
<td>9/494</td>
</tr>
<tr>
<td>Wang</td>
<td>0.030 (0.028, 0.092)</td>
<td>48/1169</td>
</tr>
<tr>
<td>Hau</td>
<td>0.023 (0.010, 0.037)</td>
<td>10/649</td>
</tr>
<tr>
<td>Marti</td>
<td>0.076 (0.032, 0.160)</td>
<td>5/68</td>
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<tr>
<td>Subgroup 5 (P&gt;0.05 %, P&lt;0.001)</td>
<td>0.074 (0.537, 0.051)</td>
<td>83/1595</td>
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<tr>
<td>Overall (P&gt;0.95 %, P&lt;0.001)</td>
<td>0.042 (0.057, 0.099)</td>
<td>172/5137</td>
</tr>
</tbody>
</table>