Review Article

Candida Species Detection in Potentially Malignant and Malignant Disorders of the Oral Mucosa: A Meta-analysis

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Abstract

Background: *Candida* species, mainly *Candida albicans*, have been related to dysplastic changes and malignant transformation of different oral mucosal lesions. **Objective:** The objective was to assess the possible influence of *Candida* detection in oral leukoplakia (OL), oral lichen planus (OLP), and oral cancerous lesions. **Search Methods:** A PubMed search through February 2018, using the following MESH terms, was performed: "*Candida,*" "precancerous conditions," "mouth," and "mouth neoplasms." **Selection Criteria:** The selection criteria included studies with findings on *Candida* detection in premalignant and malignant oral lesions. **Data Collection and Analysis:** For continuous outcomes, the estimates of effects of an intervention were expressed as mean differences using the inverse variance method and for dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratios using Haenszel–Mantel method, both with 95% confidence intervals. **Results:** Fifteen studies on *Candida* detection in premalignant and malignant oral lesions were included in this meta-analysis. Nearly 61.5% of oral cancers, 32.2% of OLs, and 29.1% of OLP lesions were infected by *Candida* species. *Candida* infection does not increase the risk for developing OL ($P = 0.32$) or OLP ($P = 0.31$). A higher mean age, male gender, tobacco consumption, and location of the lesions on tongue or floor of the mouth were factors that did not have a significant influence on developing *Candida*-infected OL. Dysplastic OLs were 10.62 times more likely to be *Candida*-infected lesions. A greater number of OL lesions infected by *Candida* species than OLP lesions were found ($P < 0.01$). Having oral cancer increased 4.92-fold risk of *Candida* infection. No statistically significant association between *Candida*-infected oral cancer lesions and *Candida*-infected OL lesions was observed ($P = 0.21$). **Conclusions:** *Candida* infection worsens the biological behavior of potentially malignant and malignant lesions of the oral cavity.

Keywords: *Candida, mouth neoplasms, oral leukoplakia, oral lichen planus*

Introduction

Although the possible association of *Candida* species with oral precancer and cancer has been widely studied, the real role of these fungi in developing these lesions has not yet been established.[1]

In the case of oral leukoplakia (OL), there is some controversy over whether *Candida* species are actually involved in its development and/or malignant transformation or they are just a coincident finding in OLs. However, *Candida*-infected OLs have a malignant transformation risk between 9% and 40%, while in noninfected OLs, this risk is lower (2%–6%).[2]

The joint action of several factors such as tobacco consumption for breakdown of epithelial integrity causes the activation of certain biotypes of *Candida* with a great capacity to produce nitrosamines, such as N-nitrosobenzylmethylamine, which can induce dysplastic changes in the oral epithelium and a greater likelihood of malignant transformation. *Candida* species are also capable of producing other substances that can contribute to oral carcinogenesis process such as acetaldehyde, proteinases, or certain pro-inflammatory mediators.[3]

According to the evidence available, *Candida* species, especially *Candida albicans*, might have an indirect etiological role in oral cancer always coupled with other etiological factors. The ability of *Candida* species to directly produce a carcinoma without the participation of other etiological factors is currently unrealistic.[4] The purpose of this study was to assess the role of *Candida* species

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detection in the biological behavior of the potentially malignant and malignant disorders of the oral mucosa.

Methods

A PubMed search of studies on *Candida* species detection related to premalignant and malignant oral lesions to February 2018 was conducted. Search strategies included the combination of the following terms from the Medical Subject Headings (MeSH): "*Candida*"(MeSH terms) AND ("precancerous conditions"[MeSH Terms] AND "mouth"[MeSH Terms]) OR "mouth neoplasms"[MeSH Terms]).

The inclusion criteria were all types of studies with results, except clinical cases; studies performed in populations not affected by certain systemic diseases or conditions (HIV infection, blood dyscrasias, diabetes, etc.); and studies with full-text availability. Exclusion criteria were studies with irrelevant or no usable data and studies with important biases.

After applying the inclusion and exclusion criteria, a total of 15 studies were included in this meta-analysis [Figure 1].

Statistical analysis

For the meta-analysis, the data were processed with the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For the continuous variables, the inverse of the variance was used for the mean difference (MD) with 95% confidence intervals (CI). For the dichotomous variables, the odds ratio (OR) was used with the Haenszel–Mantel Chi-square formula with 95% CI. Heterogeneity was determined according to the *P* values and the Higgins statistic (I^2). In cases of high heterogeneity, the random effects model was applied. The significance level was set at $P < 0.05$.

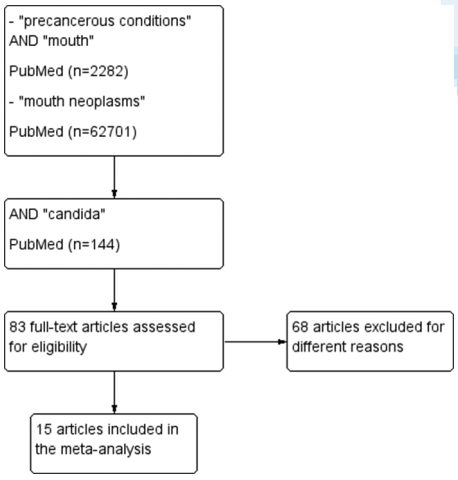

Figure 1: Study flow diagram

Results

Table 1 summarizes the descriptive characteristics of the 15 included studies in the meta-analysis.

Nine studies[6,9-15,19] assessed *Candida* species detection in OL lesions. *Candida* species were found in 347 (32.2%) out of 1078 OLs.

Three studies[14,15,6] analyzed *Candida* species detection in patients with OL and in controls without this lesion [Figure 2]. *Candida* infection does not increase the risk for developing OL, without statistically significant association (OR: 8.20 [95% CI: 0.13, 531.81], $P = 0.32$).

The possible influence of other factors related to *Candida*-infected OLs was also considered [Table 2]. A higher mean age, male gender, tobacco consumption, and location of the lesions on tongue or floor of the mouth were factors that did not have a significant influence on developing *Candida*-infected OLs. In contrast, *Candida*-infected OLs were 10.62 times more likely to be dysplastic lesions, with statistically significant differences ($P < 0.001$).

Six studies[6-8,11,12,14] investigated *Candida* species detection in oral lichen planus (OLP) lesions. *Candida* species were found in 127 (29.1%) out of 437 OLP patients.

Four studies[6-8,10] assessed *Candida* species detection both in patients with OLP and a control group without these lesions [Figure 3]. *Candida* detection was greater in patients with OLP, although no statistically significant association was found (OR: 1.79 [95% CI: 0.58, 5.55], $P = 0.31$).

Another four studies[6,10-12] evaluated *Candida* detection in patients with OLP compared to patients with OL [Figure 4].

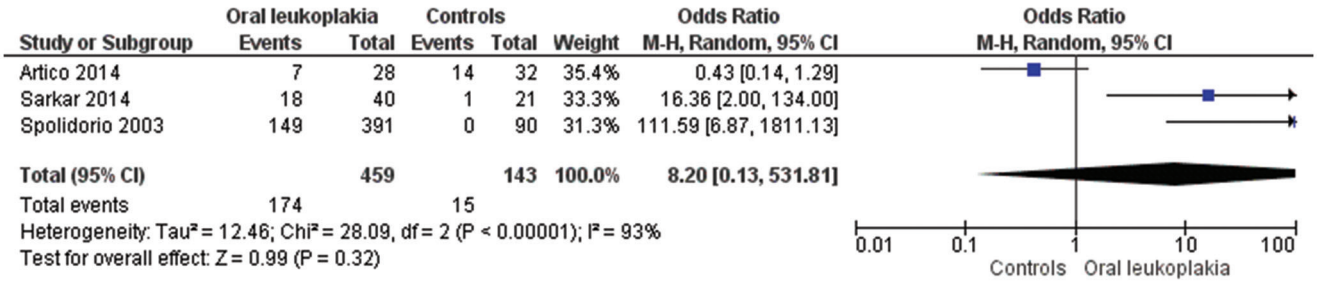

Figure 2: Study data and forest plot graph for *Candida* detection in oral leukoplakia patients and controls without this lesion

Table 1: Descriptive characteristics of included studies

Author	Year	Country	Study design	Study populations or samples	Procedures	Remarks
Nagy *et al*.[5]	1998	Hungary	Case-control study	21 OSCC 21 controls	Evaluation of the biofilm flora of the tumor surface and of the healthy mucosa	38.1% of OSCC and 0% of controls samples were infected by C. *albicans*
Spolidorio *et al*.[6]	2003	Brazil	Case-control study	391 OL 54 OLP 109 OSCC 90 controls	PAS staining of the biopsy samples	41.4% of *Candida*-infected lesions showed severe dysplasia
Zeng *et al*.[7]	2009	China	Case-control study	300 OLP 128 controls	*Candida albicans* carriage from oral isolates	44.3% of erosive forms of OLP were *C. albicans* positive
Masaki *et al*.[8]	2011	Japan	Case-control study	15 OLP 7 controls	Different *Candida* species carriage from oral isolates	OLP lesions more infected by *Candida* species, mainly non-C. *albicans* species
Rehani *et al*.[9]	2011	India	Case-control study	10 OL 10 OSCC 10 nonsmoker controls 10 smoker controls	Isolation of *Candida* species through a culture on Sabouraud's dextrose agar of oral swabs and saliva samples	More isolation of C. *albicans* in OL patients and OSCC patients No significant difference between smokers and nonsmokers
Abdulrahim *et al*.[10]	2013	Ireland	Case-control study	78 OL 110 controls	Identification of *Candida* species from oral rinse and oral swab samples using CHROMagar medium test	76.9% of OL showed moderate-to-severe dysplasia
Gall *et al*.[11]	2013	Italy	Cross-sectional study	32 OL 22 OLP 48 OSCC	PAS and GMS staining of the biopsy samples Identification of *Candida* species using API 20 C AUX system	Non- C. *albicans* species detected in 6.2% of OL, 4.5% of OLP, and 20.8% of OSCC samples
Hebbar *et al*.[12]	2013	India	Cross-sectional study	23 OL 8 OLP 10 OSCC	Oral swabs cultured on a medium not specified PAS staining of the biopsy samples	Correlation between higher *Candida* colonization and increasing severity of dysplasia
Wu *et al*.[13]	2013	China	Cross-sectional study	396 OL	PAS staining of the biopsy samples	15.9% of OL infected by *Candida* species
Artico *et al*.[14]	2014	Brazil	Case-control study	21 OL 38 OLP 32 controls	Identification of *Candida* species from oral swabs using CHROMagar medium test	Higher colonization by Candida species in controls compared to other two groups
Sarkar and Rathod[15]	2014	India	Case-control study	40 OL 21 controls	Oral swabs for stained smears and for culture on SDA with chloramphenicol	No significant difference was found between nondysplastic and dysplastic lesions according to *Candida* detection

Contd...

Table 1: Contd...

Author	Year	Country	Study design	Study populations or samples	Procedures	Remarks
Alnuaimi *et al*.[16]	2015	Australia	Cross-sectional study	104 nonoral cancer 52 oral cancer	Oral swabs for culture on SDA with chloramphenicol Identification of *Candida* species from oral swabs using CHROMagar medium test	Noncancer patients' characteristics not described
Alnuaimi *et al*.[17]	2016	Australia	Cross-sectional study	51 nonoral cancer 39 oral cancer	Identification of Candida species from oral swabs using CHROMagar medium test Ethanol-derived acetaldehyde production assay	*Candida* were more detected in oral cancer patients than nonoral cancer ones
De Sousa *et al*.[18]	2016	Brazil	Case-control study	59 OGC 32 controls	Oral swabs for culture on SDA identification of Candida species from oral swabs using CHROMagar medium test	*Candida* species from OGC patients showed better adherence to mucosal surfaces than did the control group
Dilhari *et al*.[19]	2016	Sri Lanka	Cross-sectional study	80 OL	Oral swabs for culture on SDA with chloramphenicol	Patients with tobacco consumption (smoking, betel-quid chewing) had more Candida-infected OL lesions

OL: Oral leukoplakia, OLP: Oral lichen planus, OSCC: Oral squamous cell carcinoma, OGC: Orogastric cáncer, C. *albicans: Candida albicans*, PAS: Periodic acid-Schiff, GMS: Grocott's methenamine silver, SDA: Sabouraud's dextrose agar, API: API 20 C, AUX: Yeast identification system

Table 2: Other factors related to *Candida*-infected oral leukoplakias

Factor	*n*	Reference value	MD/OR	95% CI	I^2 (%)	*P*
Mean age[10,19,13]	3	Higher in *Candida*-infected OLs patients	MD: 3.50	−1.06-8.06	61	0.13
Gender[10,19,13]	3	Male	OR: 1.41	0.79-2.53	31	0.25
Tobacco consumption[10,19]	2	Yes	OR: 1.92	0.70-5.30	48	0.21
Lesion location[10,13]	2	Lesion location different to tongue or floor of the mouth	OR: 0.79	0.27-2.35	65	0.67
Epithelial dysplasia[10,15,13]	3	Dysplastic lesions	OR: 10.62	1.98-56.82	84	<0.001*

*Statistically significant. *n*: Number of studies, MD: Mean difference, OR: Odds ratio, 95% CI: 95% confidence interval, I^2: Higgins statistic for heterogeneity

There was a greater number of OL lesions infected by *Candida* than OLP lesions with statistically significant differences (OR: 2.22 [95% CI: 1.35, 3.66], $P < 0.01$).

Five studies[5,6,16-18] considered *Candida* species detection in oral squamous cell carcinoma (OSCC) lesions. *Candida* species were found in 182 (61.5%) out of 299 OSCC patients. These same five studies[5,6,16-18] analyzed *Candida* detection in patients with OSCC and in a control group [Figure 5]. *Candida* infection was 4.92-fold more frequent in OSCC patients in comparison with controls. Statistical analysis showed highly significant differences (OR: 4.92 [95% CI: 1.98, 12.26], $P < 0.001$).

Finally, three studies[11,12,6] assessed the detection of *Candida* species in OSCC patients compared to OL patients. Although a higher percentage of positive *Candida* cases was found in patients with oral cancer, no statistically significant association was observed (OR: 1.28 [95% CI: 0.87, 1.88], $P = 0.21$).

Discussion

In the present meta-analysis on the role of *Candida* species detection in potentially malignant and malignant disorders of the oral mucosa, data from 14 studies have been included.

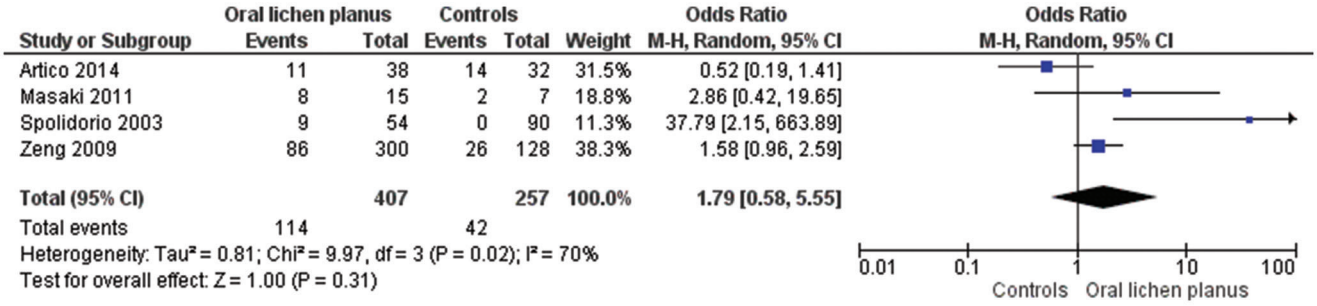

Figure 3: Study data and forest plot graph for *Candida* detection in oral lichen planus patients and controls without this lesion

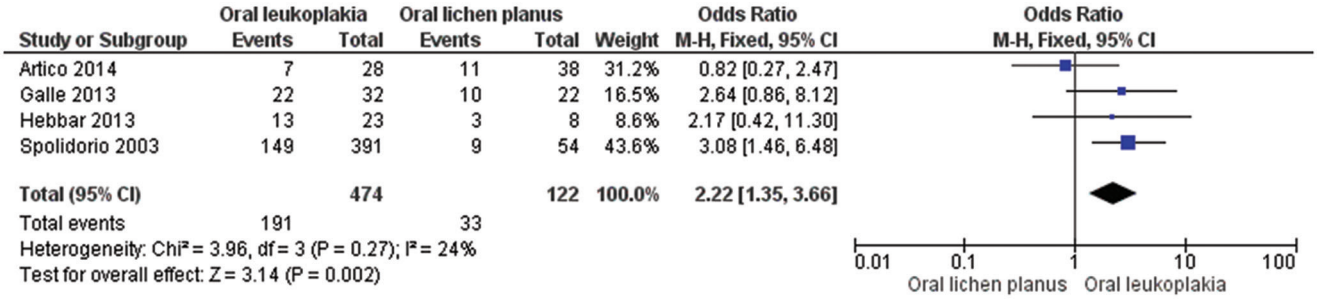

Figure 4: Study data and forest plot graph for *Candida* detection in oral leukoplakia patients compared to oral lichen planus patients

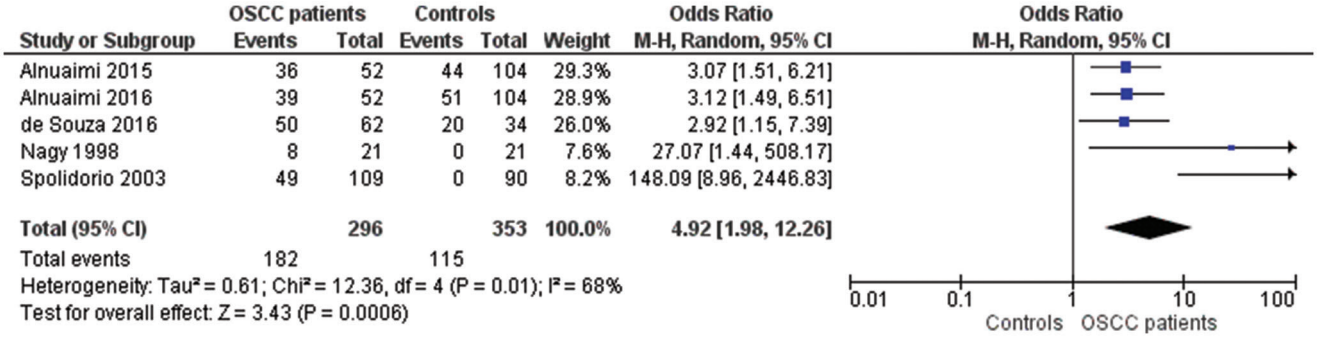

Figure 5: Study data and forest plot graph for *Candida* detection in oral squamous cell carcinoma patients and controls without oral cancer

Comparing *Candida* species detection both in patients with OL and controls, no statistically significant differences were observed. In two studies,[6,15] significantly higher percentages of patients with OL and positive *Candida* cultures than controls without this lesion were found.

However, one of these studies[15] had twice as many patients with OL than controls, whereas in the other one,[6] the population distribution by gender was very unequal. These imbalances in the populations studied have been able to affect the results. In contrast, Artico *et al*.[14] observed a higher prevalence of positive *Candida* cultures in the control group compared to OL patients. In this study, the characteristics of the two population groups were very similar and homogeneous. The presence of oral lesions did not increase the susceptibility to infection by *Candida* species.[14]

In an attempt to establish the possible influence of *Candida* infection on the biological behavior of OLs, several factors such as age, gender, tobacco consumption, and the location of the lesion or the presence of epithelial dysplasia were investigated. None of them had significant influence except epithelial dysplasia that is quite more frequent in *Candida*-infected oral leukoplakias. Three studies[10,15,13] are consistent with our results, indicating that *Candida* infection is closely related to dysplastic leukoplakias that also present a high risk of malignant transformation. *Candida* invasion may lead to epithelial dysplasia in OL. When it infects a lesion, *Candida* releases substances, enzymes, and cytokines that may induce keratinolysis and increase chorionic inflammation, altering both the epithelial cells and the epithelial architecture, producing the dysplastic changes. It would be interesting to know if the resolution of *Candida*

infection might reverse these dysplastic changes in a long-term follow-up of the lesions.[20]

Although in our study, there was a greater number of patients with OLP than controls with positive *Candida* culture, the results did not reach statistical significance. In fact, three studies[6-8] were in agreement with our results, while, Artico *et al*.[14] isolated *Candida* species in 56% of controls without oral lesions, in 29% of patients with OLP, and in 25% of patients with other oral lesions. There was a statistically significant association between positive *Candida* culture in patients without oral lesions compared to the OLP group ($P = 0.03$) and individuals with other oral lesions ($P = 0.02$). However, few studies have assessed the prevalence of oral colonization by *Candida* species in healthy controls and patients with oral lesions (mainly OL and OLP) which have proven that the presence of oral lesions by themselves does not rise the predisposition to colonization by *Candida* species.[7]

The possible role of *Candida* infection in potentially malignant lesions of the oral mucosa such as OL and OLP was also analyzed. Among the *Candida*-infected oral lesions, there was a greater number of OL patients than OLP patients with a statistically significant relationship ($P < 0.01$). Three studies[6,11,12] coincided with this result and only one[14] does not agree because a slightly higher frequency of *Candida*-infected OLP lesions (29%) compared to *Candida*-infected OL lesions (25%) was seen, although no statistical significance was found.

Regarding OSCC and *Candida* detection, we found no statistically significant association ($P = 0.15$). Five studies investigated the positive or negative *Candida* species culture in OSCC patients with oral cancer. Three of them[16-18] found significantly higher percentages of *Candida*-infected oral cancers, further evidencing that the genotypic diversity of the different *C. albicans* strains may play an important role in oral carcinogenesis.[18] However, the other two studies[5,6] observed a greater number of oral cancer cases not infected by *Candida* species, without evidencing the possible causal relationship between *Candida* detection and tumoral progression. New studies are required in larger populations that may establish the true implication of these fungi in oral carcinogenesis.[6]

In this meta-analysis, *Candida* infection was 4.92 times more frequent in OSCC patients compared to healthy controls with statistically significant differences ($P < 0.001$). Five studies[6,16-18,5] that considered *Candida* infection both in OSCC patients and healthy controls support this finding. Having oral cancer predisposes to infection by *Candida* species.

Finally, when relating OSCC patients with OL patients, more OSCC patients than OL patients had *Candida*-infected lesions, although without statistically significant influence. Two studies[12,6] coincided with our results and found more OSCC patients with *Candida*-infected lesions. In contrast, Gall *et al*.[11] found a slightly higher prevalence of *Candida*-infected lesions among OL patients, but no statistically significant association was observed. It should be considered that in this study there was a greater number of cases of premalignant lesions than cancer lesions. Moreover, these premalignant lesions showed high degrees of epithelial dysplasia, which gives them a biological behavior very close to that of neoplastic lesions. All studies point to a relevant role of *Candida* infection in the transformation and tumoral progression in potentially malignant and malignant lesions of the oral cavity.

All findings of this meta-analysis must be interpreted with caution due to the high heterogeneity of the studies included and the presence of different bias. The differences among studies could be conditioned by the study design, the methods used to collect data, the type of analysis used, the characteristics of the study populations, and samples or the duration of the studies.

Conclusions

In this meta-analysis, 61.5% of OSCCs, 32.2% of OLs, and 29.1% of OLP were infected by *Candida* species. Dysplastic oral leukoplakias were 10.62 times more likely to be *Candida*-infected lesions, with a worse biological behavior. Oral cancer increased the risk of *Candida* infection by 4.92 folds. In contrast, OLP patients did not present a raised risk than controls for *Candida* infection.

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Conflicts of interest

There are no conflicts of interest.

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