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Original Article

Dentistry Section

Role of *Candida* in the Pathogenesis of Oral Squamous Cell Carcinoma: A Systematic Review

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ABSTRACT

Introduction: Oral Squamous Cell Carcinoma (OSCC) is the sixteenth most prevalent cancer globally, with a significant proportion of cases originating in India. The progression from healthy oral mucosa to OSCC often involves Oral Potentially Malignant Disorders (OPMDs). However, recent classification updates have excluded chronic candidiasis from the list of OPMDs. Despite this, Candida species are frequently associated with cases of severe dysplasia and OSCC, suggesting a potential role in the pathogenesis of OSCC. By exploring specific pathways through which Candida may promote carcinogenesis, this review highlights the importance of recognising chronic candidiasis as an OPMD for early diagnosis and improved patient outcomes.

Aim: The present systematic review aimed to consolidate evidence on the potential association between chronic Candida infections and the pathogenesis of OSCC.

Materials and Methods: The present systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Original studies involving tumour tissues or archival blocks from patients with oral cancer and those addressing OSCC pathogenesis were included; case reports, case series, and studies using only saliva samples or oral swabs were excluded. A comprehensive search across PubMed, Scopus, and Web of Science was performed up to December 10, 2023. Study quality was assessed using the Newcastle-Ottawa Scale, with modifications to fit the review's objectives. Data extraction included information on Candida species and diagnostic approaches, with results synthesised narratively due to variability among studies.

Results: The search strategy yielded 624 articles from multiple databases (PubMed: 263; Scopus: 204; Web of Science: 157). After applying the inclusion and exclusion criteria, only 13 studies were selected for the review. Candida prevalence in Oral Leukoplakia (OL) ranged from 6.8 to 100%, with three studies reporting malignant transformation rates of 2.5%, 6.5%, and 28.7%. *C. albicans* was the most frequently detected species, followed by *C. dubliniensis*, *C. glabrata*, *C. guilliermondii*, and *C. krusei*. Some studies identified additional fungal species, though they were considered potential contaminants. Histological analysis revealed Candida hyphae penetrating deep into OSCC tissues, suggesting a role in tumour progression.

Conclusion: The review highlights the importance of recognising chronic candidiasis as an OPMD due to its potential role in the pathogenesis of OSCC. Early identification and management of chronic Candida infections could serve as a preventive strategy in high-risk populations. The findings advocate for the inclusion of chronic candidiasis in future classifications of OPMDs to enhance early diagnosis and improve patient outcomes.

Keywords: Aetiology, Candidiasis, Carcinogenesis, Dysbiosis, Malignant transformation

INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) is the 16th most common cancer, and India bears one-third of the total cancer cases globally. The incidence of new cases and death rates due to oral cancer in India is also high compared with other countries, and 70% of cases are reported only at an advanced stage, leading to a 20% five-year survival rate [1,2]. The concept of precancer was introduced in 1805, and any benign disease may develop into malignant if followed up for a long time; this is now replaced by the term Oral Potentially Malignant Disorders (OPMDs) and is defined as any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer [3]. The recent classification of OPMDs does not include chronic candidiasis [4]. On the other hand, Candida enhances cancer progression; it activates genes and signaling pathways and aids in invasion and metastasis. The association between Candida and oral premalignant lesions has been studied for a long time, but the role of fungi in these lesions and their progression has not yet been established.

The causative factors for the initiation of oral cancer are carcinogens, most commonly tobacco (smoking and smokeless forms), areca nut chewing, and alcohol consumption. Among 5,300 substances, more than 70 carcinogens have been detected in tobacco. These carcinogens are catalysed by cytochrome P450, which then forms adducts in the Deoxy ribonucleic Acid (DNA) of growth-regulating genes (TP53, KRAS), leading to unregulated growth in the cell along with oxidative stress and cytokine production [5]. However, some studies report the occurrence of oral cancer in about 4-6% of non-habitual patients, where viral infection, genetic predisposition, dietary and hormonal factors are considered predisposing factors [6,7].

The International Agency for Research on Cancer (IARC) conducted monograph programs from the early 1970s to evaluate potential carcinogens. Among pharmaceutical, industrial, radiation, and lifestyle factors, biological agents were also considered potent carcinogens [8]. Recent findings have highlighted the significant role of microbial communities in tumourigenesis. Following cholecystectomy, patients experience a notable shift in fungal microbiota, leading to increased postoperative co-morbidities, including colorectal cancer [9]. Furthermore, intratumoural fungi have been identified in pancreatic adenocarcinoma, indicating a distinct fungal mycobiome within the tumour compared with the gut or normal pancreas [10]. Additionally, *Candida albicans*, a normal commensal organism of the oral cavity, has emerged as a potential indicator and biomarker for gastric cancer in recent research [11]. Candida species, particularly *Candida albicans*, form biofilms on epithelial surfaces, triggering persistent inflammation, degrading epithelial barriers, and facilitating invasion, ultimately leading to dysplastic changes and OSCC progression [12-15]. Species-level

analysis highlighted that *Candida albicans* is the most abundant species in multiple cancers. Furthermore, community analysis found that Candida may function as a keystone taxon in the tumour microbiome, driving ecological interactions and overall variation in multi-kingdom microbial composition [16]. Previous studies have demonstrated that Candida infections contribute to cellular and dysplastic alterations in leukoplakia, a hallmark of early-stage oral epithelial carcinogenesis [17-19]. Consequently, the exclusion of chronic candidiasis from the recent World Health Organisation (WHO) classification of OPMD may necessitate reassessment. The present systematic review was devised to assess the role of Candida in the pathogenesis of OSCC.

MATERIALS AND METHODS

The present review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42022346742 and followed the PRISMA 2020 statement.

Review question: Does Candida play a role in the pathogenesis of OSCC?

PICOS:

- Population- OSCC
- Comparison- NA
- Interventions- A range of methodologies aimed at assessing the presence, load, and pathogenic mechanisms of Candida in OSCC. These included microbiological culture, molecular identification techniques such as Polymerase Chain Reaction (PCR) and quantitative PCR (qPCR), biofilm analysis, enzymatic activity assays, and studies on host interactions. Some investigations also compared the prevalence of Candida in OSCC cases with that in control groups.
- Outcome- Role of Candida in the pathogenesis of OSCC
- Type of studies- Original research

Strategy for identification of studies: An extensive literature search was performed up to December 10, 2023, with no date restrictions, in electronic databases such as PubMed, Scopus, and Web of Science.

Keywords: A thorough search was performed using Boolean operators to retrieve relevant studies. The following search terms and their combinations were applied across multiple databases:

("Carcinogenesis" OR "tumour microenvironment") AND ("biofilm metabolites" OR "Candida" OR "Candidiasis" OR "Candida albicans" OR "Moniliasis" OR "Candidosis" OR "chronic hyperplastic candidiasis" OR "chronic candidiasis") AND ("oral cancer" OR "OSCC").

Inclusion and Exclusion criteria: The inclusion criteria for this review encompassed original studies that investigated the pathogenesis of OSCC and involved tumour tissues or archival blocks from oral cancer patients. Studies were selected based on their relevance to the research question and methodological rigor. Exclusion criteria included case reports, case series, and book chapters. Additionally, studies relying solely on salivary samples or oral swabs for Candida evaluation were excluded, as Candida is a normal commensal in the oral microbiome, making it difficult to establish its pathological role in malignant transformation.

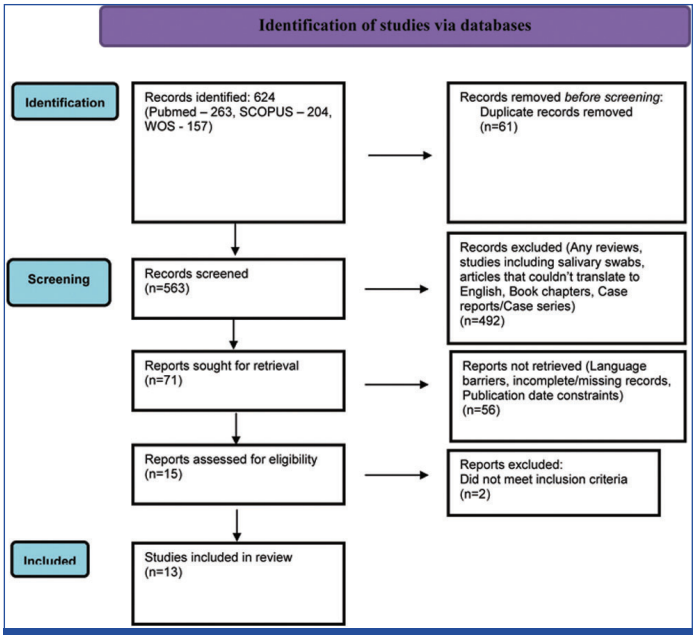
Study Procedure

Standard for selection of studies: To determine study eligibility, a structured screening process was followed. Two independent reviewers (SP and DP) screened each record and retrieved the full report to assess relevance. The selection process involved screening all identified articles independently by two authors (SP and DP), extracting key details such as country of origin, author(s), year of publication, sample size, sample type, and methods used for assessing Candida involvement. Any discrepancies were resolved through discussion to ensure accuracy and consistency in the selection of studies.

Quality assessment: The risk of bias for each included study was assessed using the Newcastle-Ottawa Quality Assessment Scale for cross-sectional and case-control studies [20]. The studies were evaluated across three key categories: selection, exposure, and comparability. A maximum of one star was assigned for each numbered criterion within the selection and exposure categories, while up to two stars could be awarded for comparability. Two authors independently assessed each study, and any discrepancies were resolved through discussion with a third reviewer. Studies receiving seven or more stars were classified as having a low risk of bias, those scoring between four and six stars were considered to have a high risk of bias, and studies with three or fewer stars were categorised as having a very high risk of bias.

RESULTS

Study selection and characteristics: The search identified 624 articles (PubMed: 263, Scopus: 204, Web of Science: 157) published across various databases. Among these, 15 articles were assessed for eligibility after full-text retrieval, and 13 articles were included in the review (tissue-based only), as illustrated in [Table/Fig-1].



[Table/Fig-1]: Flow chart of study selection adapted from PRISMA.

Among the 13 studies, 425 OSCC cases, 232 precancer cases, and 198 controls were included. Only 3 studies (23%) used special stains alone to evaluate Candida, whereas the remaining 10 (77%) involved multiple assays such as special stains, immunohistochemistry (IHC), and reverse transcription PCR (RT-PCR). Only 2 studies (15.38%) used both the control and comparison groups; six studies (46%) used only the comparison group, and four studies (30.7%) used only the control group [Table/Fig-2] [21-33].

From all the studies, Candida species were most commonly present in severe dysplasia and OSCC. Among the Candida species, *C. albicans* was predominantly associated with cancer, followed by *C. dubliniensis*, *C. glabrata*, *C. guilliermondii*, and *C. krusei* [21-23]. In a study characterising the mycobiome of OSCC, *Hannaella luteola*-like species (20%), *Candida etchellii* (32%), and *Gibberella* were predominant in OSCC [30]. These are likely contaminants of OSCC rather than members of the oral mycobiome community. Microscopically, candidal hyphae were observed deep in the connective tissue in well-differentiated and poorly differentiated OSCC.

Risk of Bias: The Newcastle-Ottawa risk of bias assessment tool for case-control and cohort studies was utilised in this review. To align with the objectives of this study, slight modifications were made to the Newcastle-Ottawa Scale (NOS). In the selection criteria, we incorporated methodological rigour in fungal identification, ensuring

S. No.	Author	Study design	Sample size	Country	Sample used	Parameters used	Statistical analysis	Inference
1.	Kumar RS et al., 2009 [21]	Case-control study	45 Precancer, 45 cancer, 45 control	India	Salivary smear and tissue samples	Gram staining, Papanicolaou, Calcofluor white	Z test, Chi-square test	*C.albicans* – Predominant, More quantity in cancer
2.	S.Tamgadge et al., 2017 [22]	Case-control study	10 Mild Dysplasia, 10 Moderate, 10 severe, 30 OSCC	India	Tissue samples	Calcofluor white, 10% KOH		Highest quantity is in cancer tissues and the least being mild dysplasia
3.	Krogh P et al., 1987 [23]	Case-control study	12 oral precancerous lesions	Denmark	Swabs from lesion and normal mucosa, biopsy for histological examination	Nitrosamine analysis, Nitrate reduction	One-way ANOVA	Nitrosation potential; *C.albicans* > *C.glabarta*, *C.parapsilosis*=0 Leukoplakias at the bottom of mouth=More dysplastic changes due to presence of precursors of nitrites and nitrates, Nodular type leukoplakia having high potential for malignant transformation has high yielding yeasts. None of the yeasts reduce nitrate to nitrite
4.	Lee CH et al., 2020 [24]	Case control study	80 tumour tissues & adjacent normal tissue from same pts	Taiwan	Tissue samples, Cell lines	GMS stain, PCR, Microarray		13.8% cases were GMS positive; however, PCR indicates 11.3% infection rate among GMS positive
5.	Jahanshahi G et al., 2014 [25]	Cross-sectional study	100 WDSCC	Iran	Tissue sample	PAS & Calcofluor White		*C. albicans* was found in 74% of cases under Calcofluor fluorescence staining, and 33 cases out of 100 were positive for PAS staining.
6.	Meyer JE et al., 2004 [26]	Cross-sectional study	8 tonsil cancer pt	Germany	Swabs and Specimen	Cell culture, RT-PCR		*C.albicans* stimulates human beta defensin-2 mRNA expression in oral epithelial cells but not in oral fibroblasts; hyperplastic tonsils have higher human beta defensin-2 mRNA than tonsillar carcinoma
7.	Hafed L et al., 2009 [27]	Case control study	Normal- 7, Oral dysplasia – 16, OSCC without lymph node metastasis- 16, OSCC with regional lymph node metastasis - 15	Egypt	Archival blocks	PAS stain, RT-PCR	McNemar test	ADH1 mRNA gene was detected in 29 specimens which stained positive for PAS
8.	McCullough M et al., 2001 [28]	Cross-sectional study	103 dysplastic/ Ca pts among 223 pts having mucosal lesion	UK	Tissue	PAS	Chi-square test	Yeasts were isolated from 77 out of 103pts (29 Moderate, 17- Moderate, 16- Severe. 15 - OSCC)
9.	Bakri MM et al., 2014 [29]	Case control study	I – Normal, II - Leukoplakia without dysplasia – 8, III - Leukoplakia with dysplasia without clinical/histological Candida – 7, IV - Candidal infection - 10 (6 with dysplasia)	Malaysia	Archival blocks	IHC, RT-PCR		Candida was detected in the surface layer but did not penetrate the deeper epithelium. All samples tested positive for Candida using both PAS and IHC staining techniques. However, Group D (dysplasia with Candidal infection) exhibited a greater abundance of Candida compared to the other groups.
10.	Perera M et al., 2017 [30]	Case control study	25 OSCC (22 after exclusion), 25 controls (Fibroepithelial polyp)	USA	Archival blocks	Nucleotide sequencing, Downstream analysis		Candida was detected in 100% of all samples and constituted 48% of the average mycobiome. *C.albicans* (100%), Hannaella luteola like species (20%), *C. etchellii* (32%) and Gibberella – predominant in OSCC.
11.	Rodriguez MJ at al., 2007 [31]	Cross-sectional study	34 Early OSCC pts (T1N0M0 – 8; T2N0M0 - 26)		34 surgical specimens from tongue and floor of the mouth	IHC – Mab C7 – 1:100 Western Blotting - Mab C7 – 1:200	Chi-square test	IHC – Highly stained – 13 cases
12.	Das SN et al., 1986 [32]	Case control study	70 OSCC pts, 40 controls	India	Delayed hypersensitivity test, Archival blocks	Candida albicans extract test		Delayed hypersensitivity test impaired in OSCC. Well-differentiated tumours show higher response. The in-vitro parameters didn't show any correlation
13.	Hsieh YP et al., 2022 [33]	Case control study	One tissue sample from Normal, OPMD with Candida, OSCC without Candida, OSCC with candida	Taiwan	Tissue sample	IHC - Stratifin, Next generation sequencing, Gene Set Variation Analysis		OSCC carcinogenesis with *C. albicans* infection is the KRAS signaling pathway and E2F target downstream genes. Stratifin - specific biomarker of OSCC with *C. albicans* infection

[Table/Fig-2]: Depicting data on the presence of Candida in Oral Squamous Cell Carcinoma (OSCC) [21-33].
OSCC: Oral squamous cell carcinoma; KOH: Potassium hydroxide; GMS: Grocott's methenamine silver; PCR: Polymerase chain reaction; WDSCC: Well differentiated squamous cell carcinoma; PAS: Periodic acid schiff; RT-PCR: Reverse transcriptase- Polymerase chain reaction; Mrna: Messenger ribonucleic acid; ADH1: Acetaldehyde dehydrogenase 1; IHC: Immunohistochemistry; KRAS- Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, E2F- Early region 2 binding factor

that studies employing robust microbiological and molecular techniques (e.g., culture methods, Polymerase Chain Reaction (PCR), qPCR) were prioritised. For the outcome evaluation, the emphasis was on the microbiological and molecular methods for Candida detection and virulence-factor assessment, rather than relying solely on clinical observations. These modifications allowed for a more precise assessment of the role of Candida in the pathogenesis of OSCC. The scoring system was based on three categories-selection, comparability, and outcome factors-that assess potential bias. A star was awarded when a study met the criteria outlined in the NOS [Table/Fig-3,4] [21-33]. Based on predetermined parameters, the summary scores were calculated and analysed. The total scores ranged from five to nine. There were two studies where a score of five was achieved, indicating a high risk

S. No.	Authors and year of publication	Selection				Comparability (comparison of cases and controls on the basis of the desi gn and analysis)	Exposure			Summary Scores
		Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response rate	
1	Kumar RS et al., 2009 [21]	**	*	*	*	**	*	*		9
2	Tamgadge S et al., 2017 [22]	*		*	*	*	*			5
3	Krogh P et al., 1987 [23]	*		*	*	*	*	*		6
4	Lee CH et al., 2020 [24]	*		*	*	*	**			6
5	Hafed L et al., 2009 [27]	**		*	*	**	*	*		8
6	Bakri MM et al., 2014 [29]	**		**		**	**			8
7	Perera M et al., 2017 [30]	*		*	*	*	**			6
8	Das SN et al., 1986 [32]	*		**		*	*	*		6
9	Hsieh YP et al., 2022 [33]	*		*		*	*	*		5

[Table/Fig-3]: Summary of bias risks and applicability concerns for case-control studies, based on the Newcastle Ottawa Quality Assessment Scale [21-24,27,29,30,32,33].
*Stands for the number of stars given for each domain, and a blank cell indicates that the study did not earn a point according to the scale

S. No.	Authors and Year of Publication	Selection				Comparability (The subject in different outcome groups are comparable based on the study design or analysis, confounding factors are controlled)	Outcome		Summary Scores
		Representativeness of sample	Sample size	Ascertainment of the exposure	Non respondents		Assessment of outcome	Statistical tests	
1	Jahanshahi G et al., 2014 [25]	*	*	*		*	**		7
2	Meyer JE et al., [26] 2004	*		*		*	*		5
3	McCullough M et al., 2001 [28]	*	*	*		*	*	*	7
4	Rodriguez MJ at al., 2007 [31]	*		*		*	*	*	6

[Table/Fig-4]: Summary of bias risks and applicability concerns for cross-sectional studies, based on the Newcastle Ottawa Quality Assessment Scale [25,26,28,31].
*Stands for the number of stars given for each domain and a blank cell indicates that the study did not earn a point according to the scale

of bias [22, 26, 33]. Only one study achieved nine stars, indicating a low risk of bias [21]. All included studies showed high-quality estimation and a low risk of bias.

DISCUSSION

Candida has long been postulated to be associated with debilitating disease, and oral candidiasis is a major problem among cancer patients. The findings of this review align with existing evidence suggesting a strong association between Candida species and the progression of OPMDs to OSCC [13,28,30]. The predominance of *C. albicans* in OSCC and severe dysplasia is consistent with previous studies that have demonstrated its role in promoting epithelial disruption, inflammation, and carcinogenesis [33,34]. Additionally, the detection of other Candida species, such as *C. dubliniensis*, *C. glabrata*, *C. guilliermondii*, and *C. krusei*, further supports the hypothesis that the fungal microbiome plays a role in oral cancer progression. The presence of fungal species like *Hannaella luteola*-like species, C. etchellii, and Gibberella in OSCC samples may represent environmental contaminants rather than key players in oral carcinogenesis, reinforcing the importance of differentiating between commensal and pathogenic fungal populations. Furthermore, the deep tissue invasion of Candida hyphae in both well and poorly differentiated OSCC suggests a more invasive role for Candida in tumour progression, potentially contributing to chronic inflammation, epithelial dysregulation, and cellular transformation.

The present review focuses on only limited mechanisms through which Candida may promote carcinogenesis, acknowledging that existing studies predominantly emphasise the identification of fungal hyphae through specific stains. The hyphal form of Candida is capable of breaching the epithelial barrier, leading to direct tissue damage and disrupting cell-cell junctions. The transition to the hyphal form may facilitate transport of precursors in saliva across the mucosal surface to epithelial cells, particularly within the stratum spinosum, where nitrosamines may initiate malignant transformation. This invasive process promotes continued colonisation and persistent infection [23]. Additionally, the peptide toxin produced by Candida hyphae has been found to inflict damage upon epithelial cells, eliciting a robust proinflammatory response that worsens tissue damage and fosters a carcinogenic milieu [35].

Notably, one significant attribute of *C. albicans* that potentially influences the development of oral cancer is its capacity to generate mutagenic levels of acetaldehyde [29]. Candida species metabolise ethanol to acetaldehyde, a potent carcinogen. Acetaldehyde can bind to DNA and proteins, forming adducts that interfere with normal cellular processes and induce mutations. Although the primary and secondary roles of *C. albicans* could not always be determined, the CaADH1 mRNA gene is associated with OSCC with or without metastasis and could not be estimated in oral dysplasia [27].

Candida infection can disrupt the normal oral microbiome, leading to dysbiosis. This altered microbial environment can further promote inflammation and create conditions favourable for carcinogenesis. Despite being considered a relatively rare component of the oral cavity microbiome, *C. albicans* functions as a keystone pathogen, exerting a significant impact on the microbiota despite its small numbers. Conversely, a few genera such as *A. tamarii* and *A. alternata*, identified in tumour samples, have been shown to possess anti-tumour activity that inhibits the growth of *C. albicans* [29].

The recent WHO classification no longer recognises candidal leukoplakia, as there is insufficient evidence to establish Candida as an independent risk factor for malignant transformation, despite its frequent presence in dysplastic epithelium [36]. The distinction between candidal leukoplakia and chronic hyperplastic candidosis is ambiguous, as both lesions do not completely disappear after antifungal treatment. Moreover, the wide range of malignant transformation rates indicates inconsistent diagnostic criteria [37]. Despite these reasons, removing such a lesion is debatable, as a grey zone still exists in understanding the role of Candida in the pathogenesis of OSCC. Only a limited number of original research studies have focused on candidal carcinogenesis using tissue samples [21-33].

Previous studies have proposed various mechanisms through which Candida may contribute to the progression of premalignant lesions into malignancy, thereby suggesting its role in carcinogenesis and invasion. Acetaldehyde is a product of Candida metabolism, with the CaADH1 gene and CaAdh1p being the enzymes responsible for intraoral production of acetaldehyde [37]. The association between Candida virulence and its activity in the conversion of alcohol to acetaldehyde has been studied, and findings suggest higher candidal metabolic activity in oral cancer patients [38,39]. Among the species, biomass and metabolic activity were higher in *C. albicans*, followed by *C. dubliniensis*, *C. glabrata*, *C. guilliermondii*, and *C. krusei*, whereas in the noncancer population, *C. albicans* and *C. parapsilosis* were found to have high metabolic activity [40]. However, advanced cancer patients have a higher prevalence of non-albicans yeasts such as *C. glabrata*, *C. tropicalis*, and *Saccharomyces cerevisiae*, which are also found in Human Immunodeficiency Virus (HIV)-infected patients [41]. The fungal species in oral cancer patients receiving both chemotherapy and radiotherapy were *C. tropicalis*, followed by *C. stellatoidea*, *C. albicans*, and *C. krusei*.

Another mechanism involves claudins, transmembrane proteins in tight junctions that promote cell-cell adhesion and interaction with fibronectin. Degradation of these proteins may cause a loss of adhesion, promoting microbial invasion and metastasis. These properties of Candida species are considered to be responsible for tumour invasion [42]. In denture wearers, the same strains produce higher amounts of proteinase and phospholipase, rendering them more capable of accelerating tumour progression [43].

Biofilm formation by *C. albicans* is considered to be a main virulence factor for carcinogenesis, akin to *Helicobacter pylori* [44]. This fungus consists of about 15% lipids, and its biofilms (in vitro) produce lipid droplets that help in invasion of tumour cells and confer drug resistance [45]. Although the cellular signaling between *C. albicans* and cancer cells remains obscure, *C. albicans* can produce nitrosamines that bind to DNA, activate oncogenes, and initiate cancer development [46].

Recently, *C. dubliniensis* has been considered among the most commonly associated fungi in patients with acquired immunodeficiency syndrome and is now found in patients with cancer. As it shares phenotypic and morphological characteristics with *C. albicans*, it is often misdiagnosed in the laboratory [47]. It has also been reported that this fungus fails to modulate NRG1 expression compared with *C. albicans*, thus depriving this species of initiating an effective invasive process [48,49].

Recent research has identified the significant role of the salivary and oral microbiome in the development of several types of cancers, including pancreatic ductal adenocarcinoma, non-small-cell lung cancer, and gastrointestinal cancer [50,51]. Additionally, it has been observed that *Candida albicans* can promote melanoma metastasis to the liver during both early and late stages of the metastatic process through proinflammatory cytokines such as Tumour Necrosis Factor (TNF)-α and Interleukin (IL)-18 [52,53]. The potential link between dysbiosis in the oral microbiome and the pathogenesis and metastasis of various cancers suggests a significant influence of the oral microenvironment on oral cancer, particularly concerning the fungal presence in the oral cavity.

The present review findings suggest that Candida infection is associated with an increased risk of malignant transformation in oral leukoplakia (OL), along with cellular and dysplastic changes. This highlights the need for further research to explore the complex interactions between Candida species and the host during the progression of OPMD. Additional studies are essential to determine whether Candida directly contributes to malignant transformation or merely thrives in a dysplastic environment, and if so, what could be its role in it. Nevertheless, the presence of Candida in OL, particularly in cases showing dysplastic changes, suggests that fungal detection could serve as a potential biomarker for assessing the risk of malignant progression.

Limitation(s)

Variations in study methodology, sample size, diagnostic criteria for Candida infection, and follow-up duration contribute to heterogeneity in findings. Furthermore, other risk factors for malignant transformation of OL, such as smoking, alcohol consumption, and genetic predisposition, were not consistently accounted for across all studies, making it challenging to isolate the specific role of Candida infection in this process. There were only limited analyses regarding non-Candida species that may play a role in dysplasia and cancer progression.

CONCLUSION(S)

Chronic Candida infections, particularly *Candida albicans*, play a significant role in the development of OSCC. Candida contributes to creating an environment that supports cancer growth by causing ongoing inflammation, producing carcinogenic substances like acetaldehyde, and damaging oral epithelial cells. The substantial evidence linking Candida species to the development and progression of OSCC strongly supports categorising chronic candidiasis as an OPMD. Further research is imperative to elucidate the precise molecular mechanisms involved and to devise effective clinical approaches to mitigate Candida's impact on oral cancer development.

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