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Revisiting the association between candidal infection and carcinoma, particularly oral squamous cell carcinoma

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Background: Tobacco and alcohol are risk factors associated with cancer of the upper aerodigestive tract, but increasingly the role of infection and chronic inflammation is recognized as being significant in cancer development. Bacteria, particularly *Helicobacter pylori*, and viruses such as members of the human papilloma virus family and hepatitis B and C are strongly implicated as etiological factors in certain cancers. There is less evidence for an association between fungi and cancer, although it has been recognized for many years that white patches on the oral mucosa, which are infected with *Candida,* have a greater likelihood of undergoing malignant transformation than those that are not infected.

Objective: This article reviews the association between the development of oral squamous cell carcinoma in potentially malignant oral lesions with chronic candidal infection and describes mechanisms that may be involved in *Candida*-associated malignant transformation.

Keywords: *Candida albicans*; *oral cancer*; *acetaldehyde*; *proinflammatory cytokines*; *inflammation and cancer*

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Infection is an important cause of cancer, causing approximately one in five malignancies worldwide (1, 2). The three main examples are infection with the bacterium *Helicobacter pylori* leading to an elevated risk of developing gastric adenocarcinoma and gastric lymphoma, infection with particular types of human papilloma virus (HPV) leading to cervical cancer, tonsillar carcinoma and some cases of oral squamous cell carcinoma (OSCC) and chronic hepatitis B and C infections leading to hepatocellular carcinoma (1–4). The herpesvirus, Epstein-Barr virus (EBV), is implicated in a range of malignancies including Burkitt's lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma and another member of the herpesvirus family, human herpesvirus 8, is a causal factor in Kaposi sarcoma (2, 3). Chronic infection with *Opisthorchis viverrine*, the Thai liver fluke and other liver flukes are associated with cholangiocarcinoma and there is evidence suggesting an association between schistosomiasis and bladder cancer (2).

There is less evidence of an etiological association between fungal infection and cancer, although for many years *Candida spp.* have been implicated in various epithelial cancers. Candidal infection does not appear to be a risk factor for dysplastic cervical lesions or cervical carcinoma (5) and most interest in *Candida* and carcinogenesis is related to oral and esophageal carcinoma. There have been a number of reports of oral or esophageal carcinoma developing in immunocompromised patients with chronic mucocutaneous candidiasis and often with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (6–9). But what evidence links candidal infection with OSCC in patients with a functional immune system? The aim of this paper is to review the association between the development of OSCC in potentially malignant oral lesions with chronic candidal infection and to describe mechanisms that may be involved.

Several *Candida spp.* are common commensal fungi that frequently can be found colonizing the oral mucosa. From cross-sectional studies, asymptomatic carriage rates in healthy individuals range from 3 to 70% but the true prevalence is probably much higher (10). Most oral

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Candida are 'opportunistic pathogens' where, depending on the local oral microenvironment or whether host defense mechanisms are compromised, they can transform from a harmless commensal to an organism causing oral mucosal infection leading to a range of conditions. Epidemiological studies have shown that when host defenses are compromised most candidal infections arise from an endogenous commensal strain rather than an exogenous strain (11, 12). This paper will concentrate on chronic candidal infection, specifically chronic hyperplastic candidiasis (CHC), sometimes also known as 'candidal leukoplakia.'

Association of *Candida spp.* with leukoplakia and chronic hyperplastic candidiasis

Cernea et al. (13) and Jepsen and Winther (14) were the first to recognize *Candida* infection in oral leukoplakias and introduced the term 'candidal leukoplakia.' Since most definitions of leukoplakia refer to it being idiopathic (15), the preferred clinical term for an adherent white patch shown to be infected with *Candida* is CHC rather than 'candidal leukoplakia.' The CHC is a form of oral candidiasis that typically presents as an adherent chronic white patch on the commissures of the oral mucosa, although other sites of the oral mucosa may also be affected. It is characterized by hyphal invasion of the epithelial surface, which usually becomes parakeratinized; the hyphae rarely extend beyond the parakeratin layer. *Candida albicans* is the most common *Candida* species present in candidal leukoplakia/CHC (14, 16) although other species such as *Candida dubliniensis*, *Candida tropicalis*, *Candida pintolopesii*, *Candida glabrata*, and *Saccharomyces cerevisiae* have been identified in these lesions (17, 18).

CHC has a propensity to undergo malignant transformation. Cawson (19) found that 6 out of 10 tissue biopsies initially diagnosed as CHC progressed to OSCC while Eyre and Nally (20) reported that 2 of 3 CHC cases underwent malignant transformation. In contrast, some CHC lesions resolve when treated with antifungals (21). Lamey et al. (22) reported a case of candidal leukoplakia with epithelial dysplasia that resolved within 11 days of systemic treatment with a triazole antifungal.

It has been shown that leukoplakia with candidal infection has a higher rate of malignant transformation than uninfected leukoplakia, with estimates that 15% of non-dysplastic CHC will progress to dysplastic lesions with 10% of these developing OSCC (23, 24). McCullough et al. (25) postulated that the progression of CHC to dysplasia is advanced by *C. albicans.* Significantly more lesions infected with *Candida* showed progressively more severe dysplasia in subsequent biopsies than occurred in subsequent biopsies from patients without candidal infection in the initial specimen (26). It has also been observed that the level of oral carriage of *C. albicans* is higher in patients presenting with leukoplakia or OSCC than in patients without oral pathology (25). Furthermore, *C. albicans* was detected in the biofilm removed from the surface of 8/21 untreated OSCC lesions but not from contiguous normal control sites (27).

It remains uncertain as to whether *C. albicans* is actually responsible for the malignant transformation in potentially malignant lesions. The presence of *C. albicans* does not necessarily prove a causal relationship and it has been argued that the presence of *Candida* in a white lesion is incidental and it has merely colonized a pre-existing lesion, due to favorable environmental conditions (14). Alternatively *C. albicans* may have a direct or indirect role in oral carcinogenesis and some *C. albicans* biotypes may contribute more to carcinogenesis than others. Arguments for and against these possibilities will be discussed below.

Attributes of *C. albicans* that may influence oral cancer development

Colonization of the epithelium

The ability of *C. albicans* to colonize, penetrate, and damage host tissues depends on an imbalance between *C. albicans* virulence factors and host defenses, often due to specific defects in the immune system (28, 29). *C. albicans* virulence factors and adherence to mucosal or artificial surfaces in the mouth have been extensively reviewed (30, 31). Two different mechanisms by which *C. albicans* can invade keratinocytes have been proposed (32). One mechanism involves the secretion of degradative enzymes by the fungus, particularly secreted aspartic proteases that can digest epithelial cell surface components and, thereby, allow the physical movement of hyphae into, or between, host cells. The second proposed mechanism is the induction of epithelial cell endocytosis (33). *C. albicans* stimulates keratinocytes to produce pseudopod-like structures that surround the fungus and draw it into the cell in a process involving the E-cadherin pathway (33). Recently, it has been shown that adhesion, invasion, and damage by *C. albicans* depends not only on fungal morphology and activity, but also on the keratinocyte type and stage of differentiation, indicating that epithelial cells differ in their susceptibility to the fungus (34). Another factor that contributes to the adhesion of *C. albicans* to mucosal surfaces is a fibrillar surface component of the yeast cell wall, a strain-specific mannoprotein layer (35–37). Several cell surface proteins have been identified as adhesins recognizing host molecules and postulated to mediate the formation of *C. albicans* biofilms *in vitro* (31, 38, 39).

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Ability to produce carcinogens and initiate carcinogenesis

Candida might induce OSCC by directly producing carcinogenic compounds, for example, nitrosamines (40). Such a carcinogen will bind with DNA to form adducts with bases, phosphate residues, and/or hydrogen bonding sites that could cause miscoding or irregularities with DNA replication (41). Point mutations thus induced may activate specific oncogenes and initiate the development of oral cancer. Krogh et al. (42) showed that some *Candida spp.* isolated from leukoplakia lesions were able to produce the potent carcinogen N-nitrosobenzylmethylamine (NBMA). The ability to catalyze the formation of NBMA was strain-dependent and these particular strains were relatively rare in the oral cavity (18). Strains with the highest potential to produce NBMA were isolated from advanced, potentially malignant, oral mucosal lesions rather than early lesions or normal oral mucosa (42). It was suggested that the tubular hyphal structure of *C. albicans* might be important as this structure allows ingress of precursors from saliva and a release of the nitrosamine product to keratinocytes, potentially initiating OSCC (42). However, in a mouse model of oral carcinogenesis Dwivedi et al. (43) found that infection with *C. albicans* alone was not capable of inducing dysplasia or OSCC.

Ability to promote carcinogenesis in initiated epithelium

C. albicans has been shown to act as a promoter of oral carcinogenesis in rat and mouse OSCC models where carcinogenesis had been initiated by repeated administration of 4 nitroquinoline 1-oxide (4NQO) (43, 44). As well as histological evidence of dysplasia in the mice exposed to both 4NQO and *C. albicans*, there was increased Ki-67 and p16 expression in comparison with mice treated with 4NQO alone or *C. albicans* alone suggesting that *Candida* creates an environment conducive to cell proliferation that may lead to clonal expansion of genetically altered cells (43).

Ability to metabolize procarcinogens

Alcohol consumption is known to be an important risk factor for the development of OSCC. *In vitro* studies with human tissue culture cells and animal studies have shown that alcohol itself is not a carcinogen (45). Rather, it is the products of alcohol metabolism that are active factors in carcinogenesis. Metabolism of ethanol results in the generation of toxic compounds such as acetaldehyde, hydroxyethyl radicals, ethoxy radicals, and hydroxy radicals (46, 47). Acetaldehyde is highly toxic, mutagenic, and carcinogenic and this effect has been shown in many cell culture studies, as well as in animal models (47–49). An increased prevalence of oral cancer is seen in certain populations with a genetic predisposition to accumulate acetaldehyde in oral tissues following ingestion of alcohol. The enzymes involved in acetaldehyde metabolism are aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH). In the mouth the conversion of alcohol to acetaldehyde can be catalyzed by ADH enzymes from the epithelium and also from oral microorganisms. Clinical studies have shown that oral fungi and bacteria may be a major source of acetaldehyde in the oral cavity (40, 50–53). Furthermore, *in vitro*, *C. albicans* cultures accumulated higher concentrations of acetaldehyde compared to other *Candida* species (54).

Acetaldehyde in the oral cavity can also come from tobacco smoking. Tobacco use, like alcohol consumption, has a definite epidemiological association with the development of OSCC, suggesting an etiological role. Tobacco smoke contains toxic aldehydes, and the combined use of tobacco and alcohol has a synergistic effect on the risk of developing oral cancer (55). Homann et al. (50) showed that tobacco smokers exposed to ethanol had a high concentration of salivary acetaldehyde. Our recent investigations (Bakri et al., unpublished observations) have revealed that Adh1p is the major *C. albicans* ADH isoenzyme catalyzing ethanol utilization and, therefore, acetaldehyde production, and that there is a constitutive expression of *C. albicans ADH1* mRNA in CHC biopsy samples. Taken together these data suggest that acetaldehyde may play an important role in the development of oral cancer. Studies assessing the effect of using the amino acid cysteine to interfere with acetaldehyde-related cancer progression have been initiated (56, 57). Cysteine binds acetaldehyde to form a stable compound thus eliminating its carcinogenic effect (56).

Ability to modify the microenvironment and induce chronic inflammation

The association between cancer and chronic inflammation has been debated for many years, but recently the role of epithelial–connective tissue interactions and the activity of chronic inflammatory cells and mediators in the tumor microenvironment has been gaining attention (58–60). Tumor growth and invasion involves multiple interactions between tumor cells and stromal cells. Among the many different stromal events that may contribute to carcinogenesis is the induction of specific proteolytic enzymes, able to degrade components of the basement membrane and/or fibrous stroma (59, 61, 62). *C. albicans* has been shown to secrete specific proteinases, capable of degrading basement membrane and extracellular matrix (63, 64). Degradation of laminin-332, a laminin present in the basement membrane associated with oral epithelium, by *C. albicans* has been described (65). *C. albicans* has also been demonstrated to degrade E-cadherin, a transmembrane glycoprotein important in adhesion of adjacent keratinocytes (66). These findings have implications not only on the potential for tissue

invasion by the organism, but on the potential to enhance the invasion of genetically altered epithelial cells, first by reducing keratinocyte cohesion and then by assisting their passage through the basement membrane.

Mucosal bacterial infection will induce chronic inflammation in the adjacent connective tissue leading to upregulation of cytokines and growth factors, which in turn may influence carcinogenesis (67, 68). This process has been well described in gastric carcinogenesis where *H. pylori* infection leads to chronic inflammation and overexpression of cyclooxygenase-2 (COX-2). COX-2 is an enzyme that converts arachidonic acid to prostanoids (prostaglandins, thromboxanes, and prostacyclins) and is strongly expressed in esophageal, gastric, and colon cancer and precancerous lesions (69). Long-term use of non-steroidal anti-inflammatory agents (e.g. celecoxib that block COX-2 production) substantially reduces the risk of these cancers (70, 71). Altered COX-2 expression, which correlated with an altered expression of cytoplasmic HuR protein (a protein that regulates the stability of COX-2 mRNA) has been shown in OSCC (72). *C. albicans* has been found to induce IL-8 secretion of endothelial cells by stimulating the cells to produce TNF-α (73). Wenghoefer et al. (74) did not detect increased expression of COX-2 or the proinflammatory cytokines IL-1β, IL-6, IL-8, IL-10, or TNF-α in biopsy specimens of leukoplakia and concluded that chronic inflammation was not involved in the pathogenesis of leukoplakia. The samples they used were homogeneous leukoplakia. Non-homogeneous leukoplakias, with a known higher risk of malignant transformation (75), were excluded and so this conclusion is not necessarily applicable to nonhomogeneous lesions infected with *Candida* or CHC.

The transcription factor NF-κB, a key coordinator of innate immunity and inflammation, is also an important tumor promoter (76, 77). It responds to signals from the toll-like receptor (TLR)-My88 signaling pathway, which is activated after tissue damage and microbial infection and can also be turned on as a result of genetic alterations in tumor cells (76). NF-κB activates genes encoding inflammatory cytokines and enzymes such as COX-2. Members of the TLR family have been shown to be important in the recognition of *C. albicans* and consequent induction of cytokines (78). Hence, candidal infection may activate particular TLRs that can communicate with the tumor promoter NF-κB. NF-κB is frequently involved in carcinogenesis where cancer-related inflammation is a feature (76). The link between *C. albicans*, TLR and NF-κB, and the production of cytokines and enzymes in the prostaglandin synthesis pathway, such as COX-2, is another potential mechanism whereby *C. albicans* might influence the development of oral cancer. This influence is likely to be exerted in the early stages of cancer development, but cancer-related inflammation is also involved in the metastasis of malignant cells (76). *C. albicans* enhanced the development of hepatic melanoma metastases in a mouse model via the elaboration of prometastatic cytokines IL-18 and TNF-α within the blood as well as in the tumor microenvironment (79).

Conclusion

Although *Candida spp.*, particularly *C. albicans*, has been implicated in oral and esophageal cancer development, the pathogenic mechanisms and its carcinogenic capability is not clearly understood. *C. albicans* is a normal commensal within the oral cavity and simply the presence of the fungal species itself does not relate to the etiology of cancers. Apart from the ability to produce carcinogens such as nitrosamine, which has been known for some time, recently other mechanisms by which *Candida spp.* may promote the development of cancer have been explored. The metabolism of ethanol to the carcinogenic acetaldehyde and the induction of proinflammatory cytokines may be important etiological factors in oral cancer development. Perhaps these new findings will generate interest in the potential association between *Candida* and oral cancer and spur controlled prospective clinical studies in this field. In the meantime the advice given by Sitheeque and Samaranayake (80), who advocated that recalcitrant CHC lesions that do not resolve after antifungal therapy should be monitored closely and who said strong consideration should be given to their removal either by conventional surgery or laser surgery, remains sound.

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