

Review Article

A Literature Review of the Role of *Candida albicans* in the Occurrence and Development of Several Cancers

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ABSTRACT

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Candida albicans (*C. albicans*) is an opportunistic fungus that usually colonizes specific parts of the human body and tends to infect hosts with immunocompromised function, including cancer patients. Several studies have pointed to the direct or indirect involvement of (*C. albicans*) in oral, esophageal, gastric, pancreatic, colorectal, liver, breast, and skin cancers. So, this article reviews the relationship between *C. albicans* and various cancers and describes the mechanisms by which this fungus may be involved in the occurrence and development of these cancers. For this reason, keywords such as: "Candida," "cancer," "oral cancer," "esophageal cancer," "gastric cancer," "colorectal cancer," "pancreatic cancer," "liver cancer," "breast cancer," "skin cancer", "risk factors" and "epidemiology" were searched. Articles published in scientific databases, such as Google Scholar, PubMed/MEDLINE, Elsevier, and Scopus, were used. In these articles, it is mentioned that *C. albicans* may play a role in the occurrence and development of various cancers via several mechanisms, such as modulation of the immune system, induction of matrix metalloproteinases, over-expression of prognostic marker genes related to metastatic events, damaging mucosal epithelium, microbiome changes, activation of oncogenic signalling pathways, induction of chronic inflammation and production of carcinogenic metabolites including nitrosamine and acetaldehyde.



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Introduction

Cancers are a group of more than 100 diseases characterized by the uncontrolled growth and proliferation of abnormal cells [1]. Cancer cells can invade normal tissues and organs and eventually spread throughout the body and may even cause the patient's death [2, 3]. According to the World Health Organization (WHO), cancer was the first or second cause of death before the age of 70 in most countries in 2015 [4]. By 2030, new cancer cases and cancer-related deaths are expected to reach 21.4 and 13.2 million people per year, respectively [5]. Overall, cancer incidence and mortality rates are increasing rapidly worldwide due to aging, population growth, and changes in major cancer risk factors, several of which are related to social and economic development [4, 5]. Most cancers fall into one of three main classifications: carcinomas, sarcomas, and leukemias or lymphomas. Carcinomas are epithelial cell malignancies and account for approximately 90% of human cancers. Sarcomas are rare solid tumors that arise from connective and skeletal tissues. Leukemias and lymphomas originate from stem cells in the bone marrow and immune system cells, respectively [5]. Although cancer can develop in almost any tissue in the body, and each type of cancer has its unique characteristics, the basic processes that cause cancer are quite similar in all types of diseases [6]. The causes of cancer are diverse, complex, and only partially known. Some external factors, such as chemicals, radiation, tobacco, food factors, lack of physical activity, obesity, environmental pollutants, and infectious organisms, as well as

some internal factors, such as hormones, hereditary mutations, immune conditions, and random mutations can play a role in causing cancers [7]. Microbial factors such as bacteria, viruses, and fungi are among the factors involved in cancer that have been investigated by studies [8, 9]. Compared to bacteria and viruses, the role of fungi in cancer has been less studied. *Candida albicans* (*C. albicans*) is a fungi that exists as a natural flora in the body, and several studies have pointed to its role in cancer [10-13]. This study was conducted to collect the information presented in the articles about the role of *C. albicans* in cancer, to help the optimal treatment of cancer patients, and to increase researchers' knowledge.

A comprehensive literature search of articles published articles was performed in the electronic databases of Google Scholar, PubMed, Scopus, Science Direct, and Springer using the terms such as: "cancer", "*C. albicans*", "oral cancer (OC)", "esophageal cancer (EC)", "gastric cancer (GC)", "colorectal cancer (CRC)", "pancreatic cancer (PC)", "liver cancer (LC)", "breast cancer (BC)", "skin cancer (BCC, SCC)", "risk factors" and "epidemiology". Irrelevant articles with invalid results were discarded. A total of 94 literary works were included in the study.

Historical background

Historical accounts linking cancer and microbes go back to four millennia ago. Clinical research on microbial effects on cancer began in 1868 with the report of tumors in patients with *Streptococcus pyogenes* infections by William Bush Regression. For a while, the role of

bacteria in carcinogenesis was discounted due to several factors, including erroneous microbiological claims, poor reproducibility, and severe toxicity in patients. At the same time, the viral theory of cancer began to develop, stimulated by the discovery of the Rous Sarcoma Virus (RSV) in 1911, which transformed benign tissue into malignant tumors in domestic chickens [8]. The association between *C. albicans* and OC was also recognized around the 1960s [14].

***C. albicans* overview**

Candida species are commensal fungi that colonize the oral cavity, gastrointestinal tract, vagina, and skin of healthy individuals [15-18]. *Candida* species are present in 400,000 systemic fungal diseases [19]. *C. albicans* is one of the most essential *Candida* species, with a carriage rate of 18.5-40.9% in healthy people, and it is responsible for about 70% of fungal infections worldwide [20, 21]. *C. albicans* can be seen in several morphological forms, including blastospores, pseudohyphae, and hyphae [22]. The transformation of yeast into hyphae is accomplished by activating a complex regulatory network of signal transduction pathways that includes many transcription factors [23]. The cell wall of *C. albicans* is made of glucan, chitin, and protein, and it has been shown that the hypha cell wall has more chitin than yeast [22]. Several pathogenic factors such as hypha production, attachment, secretion of hydrolase enzymes, biofilm formation, and growth at temperatures above 37 °C have been identified that are involved in causing disease by this fungus [23].

***C. albicans* role in cancers**

It has been shown that *C. albicans* may cause cancer via several mechanisms, namely triggering inflammation, inducing 17 responses, producing carcinogenic byproducts and using molecular mimicry [24]. Several virulence factors of *C. albicans* are involved in the development of cancer (Table 1). This fungus can lyse microflora by secreting proteolytic enzymes and, thus, reduce the host's defences [25]. It has been noted that weakening the host's immune system is associated with an increased risk of cancer [26]. Candidalysin is another virulence factor of *C. albicans*, which can play a role in many types of cancer by activating the epidermal growth factor [27]. Phenotypic transformation is another virulence factor of the yeast, leading to abnormal proliferation of epithelial cells and cause cancer by changing the structure of epithelial cells [26]. The secretion of acetaldehyde and hydrolases are other virulence factors of *C. albicans*, which can induce cancer by destroying the innate immune system and causing inflammation [28]. The role of *C. albicans* in several cancers such as OC, EC, GC, CRC, PC, LC, BC, BCC and SCC has been investigated [26], which will be explained below:

Oral cancer

OC refers to all malignancies that develop in the oral cavity, lips, hypopharynx, oropharynx, and larynx, and 90% of oral cancers are oral squamous cell cancers (OSCC) [29, 30]. OSCC is the fifth most common malignancy worldwide, along with oropharyngeal cancer [31].

Table 1. The possible role of some virulence factors of *C. albicans* in cancers

Virulence factors	Roles in candidiasis	Putative roles in cancers
Proteolytic enzymes	Damage to the cell membrane and penetration into the host cell	Decreasing host defense power through lysis of microflora
Biofilm formation	Protection of <i>C. albicans</i> against the immune system and antifungal drugs	Protection of <i>C. albicans</i> against the immune system and antifungal drugs
Candidalysin	Helping to obtain nutrients for the survival and reproduction of <i>C. albicans</i>	Activating epidermal growth factor receptor
Phenotypic transformation	Adaptation to the environment	Helping <i>C. albicans</i> in adapting to the environment and as a result attacking epithelial cells and changing their structure and abnormal proliferation
Carcinogenic molecules	Innate immune system disorder	Causing chronic inflammation

India, Pakistan, Bangladesh, Sri Lanka, Hungary, and France have the highest rates of OC. An additional 66,650 cases are reported annually in the European Union [29]. About 70% of deaths from this cancer occur in Asia [31]. Squamous mucosa of multiple head and neck structures can cause leukoplakia, erythroplakia, and leukoerythroplakia, which are all non-invasive lesions. These premalignant lesions produce several genetic mutations that trigger a chain of events that includes hyperplasia, dysplasia, and in situ and invasive cancer [29]. Chemical agents, such as alcohol and tobacco use, sulfur dioxide, asbestos, pesticide exposures, mists from strong inorganic acids, mouthwash, rubber products, and fossil fuels, biological agents including human papillomavirus, syphilis, oral and dental agents, genetic predisposition, radiation, betel quid chewing, and nutritional deficiencies have been reported as risk factors or potential causes of OC [32]. *Candida* invasion has also been reported to be an essential risk factor for the malignant transformation of oral potentially malignant disorder to OC [31]. It is mentioned that nodular leukoplakia, which is

infected with *Candida*, has a greater tendency to dysplasia and a greater tendency to become malignant [29]. Oral leukoplakia is not a rare condition; the global prevalence of oral leukoplakia is around 2.06%, with an annual malignant transformation rate of approximately 1.3% [33]. The incidence of candidal infection in oral leukoplakia has been reported between 6.8% and 100.0%. It has been noted that invasion by *Candida* hyphae contributes to malignant transformation by producing carcinogenic nitrosamines [34]. Nitrosamine compounds may activate certain protooncogenes responsible for malignant transformation [35]. Acetaldehyde is another compound that, like nitrosamines, can damage DNA and induce the growth and survival of cancer cells [27]. Acetaldehyde can also indirectly bind to glutathione, increasing reactive oxygen species' presence, stimulating chronic inflammation, and causing mitochondrial damage [14, 27]. Suppression of the immune system, chronic inflammation, and intervention in apoptosis are other candidate mechanisms in cancer development [27, 36].

Table 2. The molecular mechanism of *C. albicans* in the development of various cancers

Type of cancer	Molecular methods	Functions
Oral cancer	Acetaldehyde	DNA damage and inhibit DNA repair mechanisms, increasing the presence of reactive oxygen species, chronic inflammation
	NLRP3 inflammasome	Interference in apoptosis
	IL-17A and IL-17RA	Inflammatory cytokine release, increase in the proliferation, migration and invasion of oral cancer cells
	Programmed death-ligand 1	Inhibition of T cell activation and proliferation
	Biofilm	inducing lipid droplet formation and decreasing the efficacy of chemotherapy drugs
Esophageal cancer	Signal transducer and activator of transcription 1 gene	Immunodeficiency
	Nitrosamines	DNA damage, oxidative stress, lipid peroxidation, pro-inflammatory cytokine activation, cell death
Gastric cancer	Unknown	-----
Pancreatic cancer	Matrix metalloproteinases	Inflammatory cytokines, degradation of extracellular matrix, angiogenesis, metastasis
Colorectal cancer	IL-17A and IL-22	Chronic inflammation
Liver cancer	NLRP6	Inflammation
	Treg	Inhibiting anti-tumor immunity
Breast cancer	IL-4, IL-10, TGF- β , TNF- α	Inflammation
	Treg	Inhibiting anti-tumor immunity

IL= Interleukin; NLR= Nucleotide-binding and oligomerization domain (NOD)-like receptors; TGF= Transforming growth factor; TNF=Tumor necrosis factor; Treg= Regulatory T

Moreover, *C. albicans* has been reported to play a role in cancer by regulating the expression of programmed death-ligand 1 and thus inhibiting the activation and proliferation of T cells (Table 2) [27].

Esophageal cancer

EC is a well-known malignancy with high incidence and mortality, and its overall prognosis is poor [37, 38]. EC is the eighth most commonly diagnosed cancer and the sixth leading cause of cancer-related death worldwide. The burden of this malignancy is significantly higher in less developed areas (central and southeast Asia), and approximately 80% of cases

occur in these areas [38]. Approximately 70% of cases occur in men, and it is more common in the middle-aged and elderly population, and the risk increases with age [39]. The disease occurs in several forms: squamous cell carcinoma, adenocarcinoma, sarcomas, small cell carcinomas, lymphomas, and melanomas [38, 40]. Squamous cell carcinoma (SCC) accounts for most cases worldwide and mainly occurs in the cervical esophagus or upper and middle thoracic esophagus [38]. Smoking and alcohol consumption, improper diet, gastroesophageal reflux disease, and obesity are among the risk factors for EC [37, 41, 42]. Some changes in the

natural microbiome of the esophagus are also risk factors for this disease. Alcohol, smoking, antibiotics, and high-fat diets can cause changes in the microbiome [40]. *C. albicans* is the most common pathogen isolated from infectious esophagitis [43]. Esophageal squamous cell carcinoma is commonly seen in patients with long-term esophageal *candida* infection, especially *C. albicans* [44]. Among the mechanisms of *C. albicans* in causing cancer, we can mention the production of nitrosamines and mutations in the signal transducer and activator of the transcription 1 (*STAT1*) gene [44]. Nitrosamines are chemical compounds with low or moderate toxicity but very high carcinogenic potential [45]. Nitrosamines have been reported to be associated with stomach, esophagus, nasopharynx, bladder, and BCs [46]. *STAT1*, as a transcription factor, plays an essential role in many cellular processes, including differentiation, inflammation, apoptosis, and especially the regulation of the innate immune response and protects the cell from invading microorganisms [47]. Mutations in the *STAT1* can cause immune system defects, contributing to cancer (Table 2) [44, 48].

Gastric cancer

GC is the fifth most common cancer and the third most common cause of cancer-related deaths in the world. This cancer is a molecularly and phenotypically highly heterogeneous disease that is diagnosed histologically after endoscopic biopsy and staged using computed tomography scan, endoscopic ultrasound, positron emission tomography, and laparoscopy. High salt intake, low intake of fruit and vegetables, age, and some infections are among the risk factors for the

disease [49]. It was noted that the fungal communities in people with GC were unbalanced, with shifts in the fungal composition and a large increase in the abundance of *C. albicans* [49-51]. Therefore, it can be said that *C. albicans* can be a biomarker for GC [50]. *C. albicans* plays a role in reducing the abundance and diversity of other stomach fungi [51]. Changes in the gastric microbiome can be related to the pathogenesis of GC. However, the exact mechanism by which *C. albicans* promotes GC progression at the molecular level remains unclear [52].

Pancreatic cancer

PC is a devastating and fatal human malignancy, and there is no effective chemotherapy for it so far [53]. There are two main types of this tumor: pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumors [54]. PDAC is the most common type (more than 90%) and usually originates from pancreatic ducts, whereas PNETs originate from pancreatic islet cells [53, 54]. Most PCs are not detected until they are in their late stages due to vague symptoms such as back pain and loss of appetite that are often mistaken for other causes [54]. Familial syndromes, such as multiple endocrine neoplasia syndrome 1, von Hippel-Lindau disease, neurofibromatosis type 1, and tuberous sclerosis, poor diet, obesity, chronic pancreatitis, heavy alcohol consumption smoking, and some microorganisms are risk factors for this disease [44, 54, 55]. Among the microorganisms, several studies have mentioned the role of *Candida* species in PC [43, 56, 57]. It has been noted that people with *Candida*-related oral mucosal lesions are 70% more likely to develop PC than

others [57]. *Candida* species can enter the pancreas through the sphincter of Oddi and thus alter the pancreatic microbiome [44]. This change in microflora causes chronic inflammation and induction of matrix metalloproteinases, which play a role in the development of PDAC (Table 2) [44].

Colorectal cancer

CRC is a significant health problem both in developing and developed countries that begins in the colon or rectum and can be called colon cancer or rectal cancer, depending on the location. These two cancers are often grouped because they have many common characteristics. This cancer is among the three most common cancers diagnosed in men and women [58]. Although most CRCs occur in older people, the incidence has increased in people under the age of 50 [59, 60]. Each year, nearly one million new cases of CRC are diagnosed, and half a million deaths are recorded worldwide [60]. Obesity, physical inactivity, diets, smoking, heavy alcohol use, being older, family history of CRC or adenomatous, Lynch syndrome, Familial adenomatous polyposis, type 2 diabetes, and gut microbiota are risk factors for this disease [61, 62]. The gut microbiota maintains intestinal homeostasis and functions and is often considered the first line of defence against various pathogens [62, 63]. The gut microbiome is responsible for synthesizing several important vitamins for our human body, such as folate, biotin, and cobalamin, which promote anti-inflammatory properties [64]. The composition of the gut microbiome is dynamic and changes throughout our lives under the influence of many factors, namely diet, stress, antibiotics, and

inflammation [63]. *C. albicans* is part of the intestinal microbiota and has been mentioned as a potential screening tool for people at risk of developing CRC or in the early stages of the disease [65]. *C. albicans* is thought to contribute to CRC progression through its effects on the immune system [27]. *C. albicans* increases the level of glycolysis in macrophages via the hypoxia-inducible factor-1 (HIF-1) pathway and causes the secretion of Interleukin (IL)-7 and its release from macrophages [29]. Increased IL-7 effectively upregulates the expression levels of STAT3 and aryl hydrocarbon receptor transcription factors in the gut lymphocyte 3, which then increases the level of IL-22 secretion, thus promoting intestinal epithelial cell proliferation and CRC progression (Table 2) [29].

Liver cancer

LC is the fourth leading cause of cancer death worldwide, and its incidence and mortality rates are steadily increasing [66]. It is thought that by 2025, more than 1 million people will be diagnosed with primary LC annually, which poses a serious health challenge and societal burden [67]. About 90% of LC cases are hepatocellular carcinoma and 10-15% of cases are cholangiocarcinoma [66, 68]. The variety and complexity of these malignancies make their early diagnosis and the development of treatment methods difficult [66]. So far, the main treatments have included surgical resection, liver transplantation, radiofrequency ablation, transarterial embolization, transarterial chemoembolization, and systemic therapy with molecularly targeted agents [69-71]. Despite significant advances, these treatments have not

been able to provide satisfactory results due to high heterogeneity, frequent relapse, and drug resistance [72, 73]. Cirrhosis, lifestyle, aflatoxins, alcohol drinking, obesity, hereditary tyrosinemia, alpha-1- antitrypsin deficiency, non-alcoholic fatty liver, genetic predisposition, diabetes, autoimmune liver disease, and various infectious agents are risk factors for this disease [66, 74-77]. Among infectious agents, *C. albicans* is closely related to LC [29]. One study showed that the diversity of the intestinal fungal community in patients with LC was significantly reduced, and the abundance of *C. albicans* was increased [78]. *C. albicans* has been shown to increase tumor weight and size and increase the expression of nucleotide oligomerization domain-like receptor family pyrin domain containing 6 (NLRP6) in the intestinal tissues [78]. The harmful effect of *C. albicans* on LC may be via NLRP6 [78]. It has been shown that *Candida* can cause tumor progression through the induction of regulatory T (Treg) cells and cytokine changes [79]. Treg cells are a subset of CD4+ T cells that are required to control autoimmunity, reduce excessive inflammation caused by the immune response to pathogens, and maintain maternal and fetal tolerance [80]. Treg cells play a role in tumor development and progression by inhibiting anti-tumor immunity (Table 2) [81].

Breast cancer

BC is a pathological condition in which cells in the breast grow out of control [82]. In most cases, the disease occurs from the milk ducts, while other minor cases occur from the lobules [83]. Cancer of the ductal area is known as ductal carcinoma, while cancers involving the

breast lobules are called lobular carcinoma [84]. BC is the most common female malignant tumor in the world and is very common in less developed countries [83, 85]. About 99% of this cancer is seen in women, and only 1% of its cases are seen in men [85]. Sex, age, degree of economic development, hormonal status, hormonal contraception, the age of birth of the first child, the number of children born, genetic factors, ionizing radiation, alcohol consumption, diet, obesity, chronic nicotine, and infection with *C. albicans* are risk factors for this disease [85-92]. *C. albicans* appears to be effective in BC through the upregulation of Treg cells and dysregulation of the cytokine network [93]. It has been shown that *C. albicans* can decrease the ratio of interferon- gamma (IFN- γ)/ IL-4 and increase the levels of IL-10, transforming growth factor- β , and tumor necrosis factor alpha, effectively increasing tumor growth (Table 2) [79].

Skin cancer

Skin cancer is one of the most common types of cancer, and its incidence is increasing, which will create a major burden on healthcare systems [93]. Skin cancer is classified into two categories: melanoma skin cancer (MSC) and non-melanoma skin cancer (NMSC) [94]. NMSC is the most frequently diagnosed type of cancer, and MSC is associated with the highest number of deaths [94]. Sunlight, ultraviolet radiation, solid organ transplants, and some microorganisms are risk factors for skin cancer [44, 94]. Unlike the cancers mentioned above, there are very few studies on the relationship between skin cancer and *Candida* infections, and most epidemiological aspects have been

investigated [12, 27]. In addition to fungal infection, antifungal treatment may also contribute to skin cancer [44]. Recent research showed that voriconazole significantly increases the risk of SCC by about 2.6-fold in a dose-dependent manner [44].

Discussion

As mentioned, *Candida* plays a role in various cancers. Although several mechanisms have been suggested for the role of *Candida* in cancers, the mechanisms employed by *C. albicans* in the development of various cancers are still under investigation. However, to investigate this issue further, it is necessary to understand the pathogenicity of *C. albicans*, including its virulence factors and interaction with the host's immune response. Cancer of the oral mucosa is one of the diseases in which the role of *Candida* has been mentioned [95]. Nevertheless, some studies have rejected the independent role of *Candida* species and suggested that these microorganisms play an indirect role along with other factors, such as smoking and tobacco [95, 96]. What is important is that *Candida* plays a role in the development of OC independently or dependently on phenotypic and genotypic changes [32]. There are several reports of EC following esophageal candidiasis [27, 97]. Although the mechanisms of EC development are valid, this link is still weak and anecdotal. Due to the high risk of malignancy in patients with chronic candidiasis, careful surveillance for early detection of esophageal carcinoma seems essential [27]. In GC patients, an increase in fungi such as *C. albicans*, *Fusicolla acetilerea*, *Arcopilus aureus*, and *Fusicolla aquaeductuum* and a decrease in fungi, including *Aspergillus montevidensis*,

C. glabrata, *Penicillium arenicola*, and *Saitozyma podzolicahave* have been reported [51]. Although the role of *Candida* in causing GC has been mentioned, the exact mechanism by which *C. albicans* promotes this cancer progression at the molecular level remains unclear and needs further investigation [52]. CRC is another disease in which the role of *Candida* has been mentioned [27]. Changes in mycobiota have been reported in CRC [98]. In addition, a study showed a distinct microbiota in the early and late stages of CRC [99]. *C. albicans* was also found to be closely associated with LC [29]. *C. albicans* has been shown to promote the progression of LC through changes in the metabolism of cancer cells [78]. BC is another important cancer in which the role of *Candida* has been mentioned. It is mentioned that *C. albicans* increases tumor growth by disrupting the balance of the cytokine network [79].

Conclusion

This study highlighted the possible role of *C. albicans* in several cancers. This study is expected to increase our understanding of the role of *C. albicans* and its mechanisms in carcinogenesis and cancer prevention and treatment. Although many studies have studied the role of *Candida* in cancer, most of these studies are epidemiological surveys, and its molecular mechanism has been poorly studied. So, it was discovered from the review of articles that *C. albicans* mainly play a role in various cancers by causing inflammation.

Overexpression of metastatic genes and changes in epithelial-mesenchymal transition markers are other ways of this microorganism in causing cancer. OC is one of the most common types of

malignancy, and many studies have investigated the role of *C. albicans* in its development. Skin cancer is one of the cancers that few studies have investigated the role of *C. albicans* in its development, and despite the increase in the colonization of this fungus in this cancer, its molecular mechanism is not known, and only the role of voriconazole has been mentioned. In some studies, it is still in doubt that *C. albicans* causes cancer or that cancer increases the colonization of this fungus. Future studies should focus on prospective designs with long-term follow-up to assess the association between *C. albicans* infections and various cancers, considering confounding factors. Future studies should focus on identifying biomarkers of

C. albicans infection to detect the initiation of carcinogenesis.

Ethical Considerations

All ethical considerations were followed in compiling this work.

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Conflicts of Interest

The Author declares no conflict of interest.

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Authors' Contribution

MT performed sample collection, data curation, data analysis and wrote the manuscript draft, edited and approved the final manuscript.

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