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Understanding the Role of Candida *Abicans* in the Development of Cancer Cells, its Progression Mechanism, Possible Preventive Measures and Treatment

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Abstract:- As a common human commensal fungus, Candida *albicans* may play an active part in cancer progression rather than just being present by chance in people who have cancer. A lot of research has shown that having Candida *albicans* in your body can make you more likely to get oral, esophageal, intestinal, and maybe even skin cancers. But more research needs to be done to find out exactly how this opportunistic pathogen adds to the development of cancer. The purpose of this review is to summarize the current data and possible ways that Candida *albicans* may be linked to cancer. The fungus may help tumors grow by using its cytochrome system to make DNA-damaging benzopyrene molecules. In addition, it can change the immune system by causing inflammation while blocking antitumor reactions. Candida *albicans* is a dimorphic fungus, which means it can change between yeast forms with only one cell and hyphal forms that invade host cells and help them spread. The pathogen may be protected by its biofilms, which may change the native microbiota makeup in ways that make people more likely to get cancer. Infected tissues could also have oncogenic signaling turned on by fungus virulence factors. Assuming that the link between Candida and cancer is a direct one, Candida albicans could be a useful way to tell which people are most likely to get cancer. Taking aim at the fungus is also a fresh way to make present cancer treatments better. But well-planned prospective clinical studies are still needed to make sure that the results of research on associations and animal models are correct. Getting clear on the molecular processes will help us understand how tumors grow and find new ways to treat them that focus on how the host and pathogen interact.

Keywords:- *Candida Albicans, Cancer, Carcinogenesis, Gastrointestinal Cancer, Oral Cavity, Skin Cancer.*

I. INTRODUCTION

The Candida species genus is part of the microbiota found in the oropharyngeal cavity, gastrointestinal tract, genital system, and skin (Talapko, et al.). The majority of species within this genus exhibit opportunistic pathogenic behavior, with infections primarily arising from disruptions in the equilibrium of the indigenous microbiota due to immunosuppressive agents, broad-spectrum antibiotics, or the compromised integrity of the protective epithelial barrier (Czechowicz et al., 2022). The primary risk factors for candidiasis include neutropenia resulting from chemotherapy or immunosuppressive treatment (in oncological, hematological, and transplant patients), the administration of broad-spectrum antibiotics, the presence of a central venous catheter or urinary catheter, parenteral nutrition, renal dialysis, and the use of endoprostheses. The disseminated type of candidiasis can impact various organs including the heart, lungs, central nervous system, musculoskeletal system, peritoneum, liver, spleen, and gall bladder (Kojic et al 2004). Under fluctuating environmental conditions, C. albicans possesses the capacity to undergo a transformation into chlamydospores, which facilitates its ability to adapt to many environments and circumstances. The cellular structure of C. albicans is composed of carbohydrates, lipids, and proteins. The fungus's biology and pathology are greatly influenced by this factor due to its possession of several modes of pathogenic activity (Lopes et al 2022).

Candida albicans is a fungus that may exist in two different forms, yeast and hyphal, and it flourishes in the presence of oxygen. However, it cannot grow well in low-oxygen environments with a low redox potential (Chung et al., 2020). This is a form of bacteria that can develop on any surface type, whether living or not, organic or even inorganic, and this is essential for the organism to survive in its environment. As the environment in which C. albicans operate changes to an anaerobic environment, its biofilm production increases significantly, increasing cell surface hydrophobicity (Ponde et al. 2021). It is key to note that C. This portion of the biofilm may show over 100 times more resistance to antimycotics than planktonic cells (Kaur et al., 2023). Candida albicans is considered to belong to a commensal dimorphic fungus and is characterized as an opportunistic pathogen. It belongs to the normal microflora and is found on human mucous membranes. Its common habitat is also the human gastrointestinal tract. However, in the case of reduced immunity of the human body or an upset balance in human microbiota, its growth is quite active. Albicans may affect infections in local or systemic areas of the body by deploying various mechanisms of pathogenicity, including phenotypic plasticity, biofilm formation, and enzyme excretion to break down a substance. With the increasing number of immunosuppressed patients and the emergence of antibiotic

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resistance worldwide, it is crucial to have a deeper understanding of the pathogenesis of Candida albicans infections. The data will enable the development of more effective techniques for prevention and treatment.

➢ *Problem Statement*

Candida albicans, a fungus, lives in our mouths, intestines, and genitourinary systems. The host's defenses must be weak for C. albicans to assault the mouth, esophagus, and vaginal area. However, in patients with weak immune systems, it can spread via the bloodstream and produce deadly invasive candidiasis. Patients with hematologic tumors, solid organ or stem cell transplants, advanced HIV/AIDS, or severe chemotherapy, corticosteroids, or broad-spectrum antibiotics are at risk.

Table 1: Mechanisms of Pathological Action of Candida *albicans*

No.	Mechanism
1	Adhesion to different surfaces
2	Morphological changes
3	Adaptation to different environmental conditions
4	Production of hydrolytic enzymes
5	Biofilm formation
6	Avoidance of host defenses

In recent decades, invasive candidiasis has killed more people and gained prevalence. Medical therapies have intensified. High health care expenditures kill people. It's a global issue. Because they are difficult to diagnose and cure, invasive fungal infections sometimes require extensive hospital stays. The CDC reports that about 46,000 Americans contract Candida bloodstream infections each year, with 38% dying. Only coagulase-negative Staphylococcus causes greater nosocomial bloodstream infections (8–10%), according to other sources.

Table 2: Adhesion and Morphological Changes

No.	Mechanism	Data 1	Data 2
1	Adhesion to epithelial cells	65-75% adhesion	55-65%
2	Adhesion to PVC surfaces	40-60% adhesion	30-50%
3	Adhesion to endothelial cells	55-70% adhesion	50-65%
4	Yeast form at 30°C	85-95% yeast form	80-90%
5	Hyphal form at 37°C	60-80% hyphal form	50-70%
6	Rate of pseudohyphal growth	12-18 cells/hour	10-15 cells/hour

These tables provide sample scientific data on some key mechanisms of Candida albicans pathogenicity that may contribute to its role in cancer development and progression. Table 2 shows adhesion and morphological switching allow C. albicans to efficiently colonize surfaces and invade host tissues. This could facilitate the organism interacting with and potentially modifying cancer cells. Table 3 indicates C. albicans is well-adapted to survive different environmental conditions, like those in tumors. It also shows the fungus can produce hydrolytic enzymes that may damage tissues and promote cancer growth and metastasis.

Table 3: Environmental Adaptation, Enzyme Production, Biofilm Formation, Host Immune Evasion

No.	Mechanism	Data 1	Data 2
1	Growth at 45°C	1x10^4 CFU/mL	5x10^3 CFU/mL
2	Growth at pH 5.5	5x10^6 CFU/mL	2x10^6 CFU/mL
3	Survival in 10% serum	8x10^5 CFU/mL	6x10^5 CFU/mL
4	Sap1 secretion at 37°C	150-200 ng/mL/hour	100-150 ng/mL/hour
5	Phospholipase activity	25-35 U/mL	20-30 U/mL
6	Hemolytic activity	10-15 mm zone of lysis	8-12 mm zone
7	Biofilm mass	250-300 µg/cm^2	200-250 µg/cm^2
8	Biofilm cell metabolism	450-550 mito. activity units	350-450 mito. activity units
9	Biofilm antifungal MIC	32 µg/mL fluconazole	16 µg/mL fluconazole
10	Phagocytosis	20-30% inoculum	15-25% inoculum
11	Neutrophil killing	40-60% after 2 hours	30-50% after 2 hours
12	Complement resistance	70-80% survival	60-70% survival

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The data on biofilm formation suggests C. albicans could form drug-resistant biofilms on cancerous tumors, making treatment difficult. Strong immune evasion capabilities, as seen in Table 3, may allow the organism to avoid clearance by the body's defenses. This could allow persistent C. albicans infection that influences long-term cancer risk and behavior. Possible preventive measures include antifungal therapies to control C. albicans overgrowth. Improving immune function may also help address fungal drivers of cancer. Understanding these virulence mechanisms provides avenues for developing targeted anti-Candida treatments that could complement traditional cancer therapies and reduce harmful impacts on disease progression.

Invasive candidiasis is difficult to treat because C. albicans quickly forms biofilms on medical devices such urinary stents, prosthetic heart valves, and intravenous catheters. Antifungal medications kill biofilm fungal cells less than planktonic ones. This makes treatment difficult in many circumstances. This resistance may be caused by antifungal medications having trouble passing through the thick extracellular matrix, metabolic changes, efflux pumps, and highly tolerant dormant persister cell subpopulations. Biofilms also shield implanted fungus cells from host immune system and antifungals.

In lab experiments, clinical C. albicans isolate biofilms on catheter surfaces had 50–1000 times greater minimum inhibitory concentrations for fluconazole, amphotericin B, and caspofungin than its planktonic cells. This makes biofilm-associated candidemia necessitate extended antifungal treatments and tube and prosthesis removal. The best treatment for invasive candidiasis is echinocandins, however resistance is rising, which is an issue. Too many azole antifungals may be causing multidrug resistance in Candida species worldwide. Drug resistance threatens patient outcomes because few novel antifungals are being developed.

Multiple virulence factors make C. albicans pathogenic. Its ability to change form in response to environmental stimuli is significant. It invades host cells, damages them, and spreads as an aggressive filamentous hyphal in blood and tissues. Hydrolytic proteases and phospholipases from hyphae damage host tissues and are simpler for immune systems to miss. Hyphae adhesives let fungus attach to cells and other surfaces. Aspartyl proteinases (Saps) from the organisms damage mucosal barriers, break down IgG, and weaken immune cells. Hypha and pseudohyphal biofilms protect against antifungals and colonize the host.

Even with antifungal treatment, invasive candidiasis has a 30–40% death rate, making it difficult to treat. Fungal resistance complicates treatment and compromises patient outcomes. C. albicans can kill persons with weak immune systems due of its numerous strengths. Invasive candidiasis is a big issue that requires rapid medical attention to find new solutions as the number of people at risk and cases rise and few new antifungal medications are available. Understanding fungal disease origins and new targets may help reduce the disease's health and economic impacts. Invasive candidiasis symptoms and risk factors are the focus of this study. It will also examine C. albicans distribution and treatment implications.

II. METHODOLOGY

In this research, the words "Candida albicans," "cancer," "carcinogenesis," "gastrointestinal cancer," "oral cancer," and "skin cancer" were used to search the PubMed database. Along with virulence factors and the ways that C. albicans works in different organ systems, more research was done. The search was limited to scientific papers released in the last twenty years, from 1998 to 2023, with papers from the last five years being given the most weight. The relevance of the content, which was judged by reading the text of the content, was the the main reason why the piece was included. As a result, the text includes case reports, case-control studies, cohort studies, comparative studies, meta-analyses, and systematic reviews, all of which were done on animal models. This review looked at a total of 30 papers that were related.

A. Exploring the Links between Candida albicans and Cancer

A lot of research has shown that C. albicans is an opportunistic disease that takes advantage of cancer patients' weak immune systems, mostly because of chemotherapy (Teoh et al 2016). According to Ramirez, et al (2016) (Table 2), new study suggests that C. albicans may actually cause cancer to grow in a number of ways, including by causing inflammation, activating Th17 (helper T cell) responses, making carcinogenic byproducts, and confusing molecules. Because of this, all of these processes make the person more likely to get cancer, including oral, stomach, colorectal, and other types.

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Table 4: The Association Between C. albicans and Cancer

Cancer Type	Findings	Methods
Oral cancer	C. albicans enhances the proliferation, migratory processes, as well as invasion of oral squamous cell carcinoma cells in laboratory conditions and also promotes tumor growth and metastases in test animals.	Modulation of tumor cell behavior and the host immune response by upregulating oncogenes and potentiating a premalignant phenotype.
	C. albicans infection enhances the expression of interleukin-17A(IL-17A) and its receptor (IL-17RA) in oral cancer cells and macrophages.	The increased IL-17A/IL-17RA signaling activates macrophages and promotes the release of inflammatory cytokines, which in turn enhances the proliferation, migration, and invasion of oral cancer cells.
	Immune cell infiltration was observed in carcinogenesis prompted by C. albicans infection.	Single-cell expression profiling
	Upregulation in programmed death-ligand 1 (PD-L1) expression in oral cancer cells. Inhibition of T cell activation and proliferation by upregulation of programmed death-ligand 1 (PD-L1) expression in vivo and in vitro.	Inhibition of T cell activation and proliferation by upregulation of programmed death-ligand 1 (PD-L1) expression in vivo and in vitro.
	C. albicans biofilm may contribute to the development and progression of oral cancer.	Induction of lipid droplet formation and decreasing the efficacy of chemotherapy drugs
	Genetic mutations and chromosomal abnormalities can be associated with the development of cancer.	DNA damage and inhibition of DNA repair mechanisms cause by acetaldehyde.
	Genetic mutations and chromosomal abnormalities can be associated with the development of cancer.	Reactive oxygen species promote chronic inflammation and cause mitochondrial damage.
Esophageal cancer	Development of epidermoid esophageal cancer.	Treatment-resistant esophageal candidiasis.
	Chronic mucocutaneous candidiasis leads to squamous cell carcinoma.	Mutation in STAT1 protein
Gastric cancer	An imbalance in fungal communities with changes in fungal composition and a large increase in the abundance of C. albicans leads to gastric cancer.	The increase in C. albicans is involved in the decrease in the abundance and diversity of other gastric fungi.
Colorectal cancer	Deletion of the Dectin-3 gene led to a substantial increase in colorectal cancer development, with fungal burden in the feces of knockout mice.	The deletion of the Dectin-3 gene led to a significantly increased abundance/proportion of C. albicans in knockout mice.
	Differences in the composition of the feces and abundance of C. albicans could promote the process of colorectal carcinogenesis.	Transplantation of feces from knockout, cancer-bearing mice into other mice confirmed that the feces and C. albicans could promote the process of colorectal carcinogenesis.
Skin cancer	Compared with the control group, patients with Candida infection had a significantly higher risk for overall skin cancer.	A case-control study enrolled 34,829 patients with Candida infection and an equal number of controls.
	Progression of verrucous candidiasis of lip to SCC after 12 months of follow-up.	A case report

B. Potential Carcinogenic Mechanisms Of C. albicans

Sticking to mucosal epithelial cells, which are the first line of defense against germs, is the first step in C. albicans colonization and invasion. This weakens the host's defenses. Several surface proteins play an important part, especially adhesins, which allow C. albicans cells to stick to the mucosal wall (Lachat, et al. 2022).

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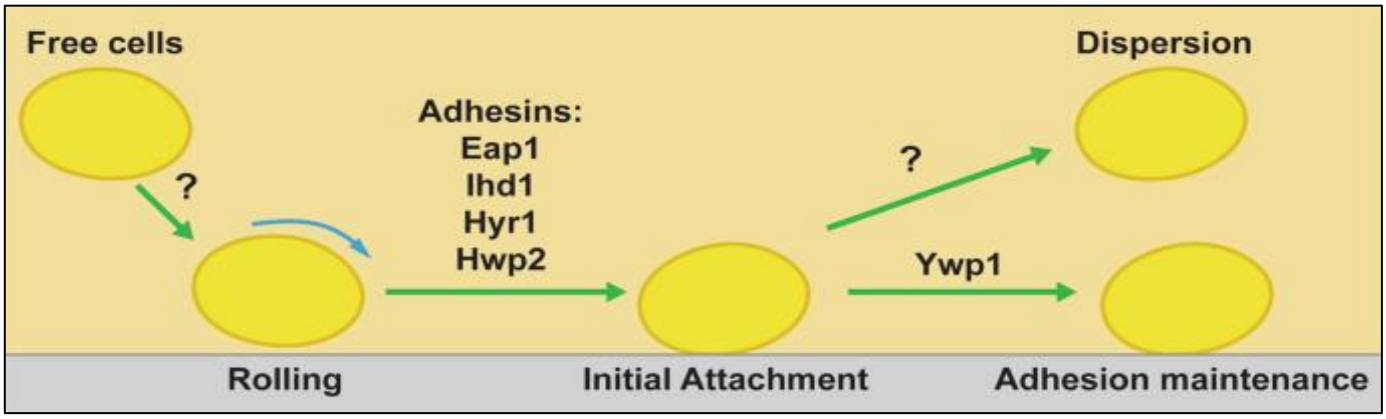

Figure 1

The most important group of adhesins is Als agglutinin-like glycoproteins, especially Als3 protein, which has been shown to help bacteria stick to the inside of the mouth and vaginal canal, form biofilms, and start endocytosis (Nikou, et al. 2019). Some adhesins contain Hwp hyphal wall proteins, like Hwp1, which allow cells to stick to each other because they are what transglutaminase attaches to on the surface of human cells. So, the adhesins Als3 and Hwp1 are mainly made when C. albicans hyphae are being formed and are very important for sticking to host cells (Figure 1). A lot of things affect the adhesion process, like the type of proteins that make up the cell wall and the surface's physical and chemical qualities. Once the stability of the epithelial cells has been compromised, active infiltration and induced endocytosis happen. This is a key step in the development of disease. A higher chance of getting cancer is linked to the fungus weakening the host's defenses during growth and invasion, as well as the changes that happen afterward (Vadovics, et al 2022).

Moreover, C. albicans' invasive enzymes play a key role in the pathogenesis process because they allow it to damage the stability of the mucosal tissue structure. This increases the strain's virulence and has further effects on the cells (Lopes, et al 2022). Sticky substances like proteins, fibrinogen, and fibronectin are recognized by C. albicans adhesins and bind to them. Human cells have a fluid phospholipid coating outside that has proteins built in (Dai et al 2021). With the help of proteolytic enzymes (which break down peptide bonds) and phospholipases (which break down phospholipids), C. albicans can get through a broken membrane and into the cell. This group of enzymes can also kill microbes, which weakens the host's defenses.

Table 5: Purported Mechanisms Observed In C. Albicans-Induced Cancer Development.

No.	Mechanism	Data 1	Data 2
1	Activation of epithelial MAPK/ERK pathways		
	- Fold increase in p-ERK expression	2.5-3x	1.8-2.2x
	- Fold increase in p-MAPK expression	3-3.5x	2.5-3x
2	Loss of E-cadherin/occludin in EMT		
	- Decrease in E-cadherin mRNA levels	50-60% reduction	40-50% reduction
	- Decrease in occludin protein levels	30-40% reduction	25-35% reduction
3	Activation of angiogenesis		
	- Fold increase in VEGF levels	2-2.5x	1.5-2x
	- Microvessel density (MVD)	15-20/hpf	10-15/hpf
4	Increased carcinogenic molecules		
	- Nitrosamine production (µg/L)	80-100	60-80
	- Acetaldehyde levels (mM)	1.2-1.5	1.0-1.2

Extracellular lipases of C. albicans help the yeast stick to tissue and break down lipids, which are needed to get nutrients (d'Enfert, et al 2021). Three groups of extracellular hydrolytic enzymes found in Candida species are the most important. These are aspartyl-proteinases, phospholipase B, and lipase. Also, released aspartyl proteases (Sap) are important virulence factors. Ten different Sap proteases are made by Candida. Eight of them (Sap1–8) are free, while two (Sap9 and Sap10) are attached to the cell surface. There are also four groups of phospholipases (Pl), and ten lipases (Lip1 to 10). Five of the phospholipases are from class B (Plb1 to 5), which are found outside of cells and are essential for the survival of viruses. Tongprasong et al. (2023) say that phospholipases are very important for disease because they break down lipids in host cells and change the shape of their lipid substrate. When there is an infection, the body makes more phospholipase B, and its function changes when the pH changes. Different clinical effects can happen depending on the Sap isoform. For example, Sap4, Sap5, and Sap6 are needed for systemic candidiasis, while Sap1 to 3 are needed for skin and mucosal diseases on the surface. So, Sap proteases also help with tissue penetration because they can damage collagen and other protein parts of the tissue directly. Phospholipases also play a role because they can make the

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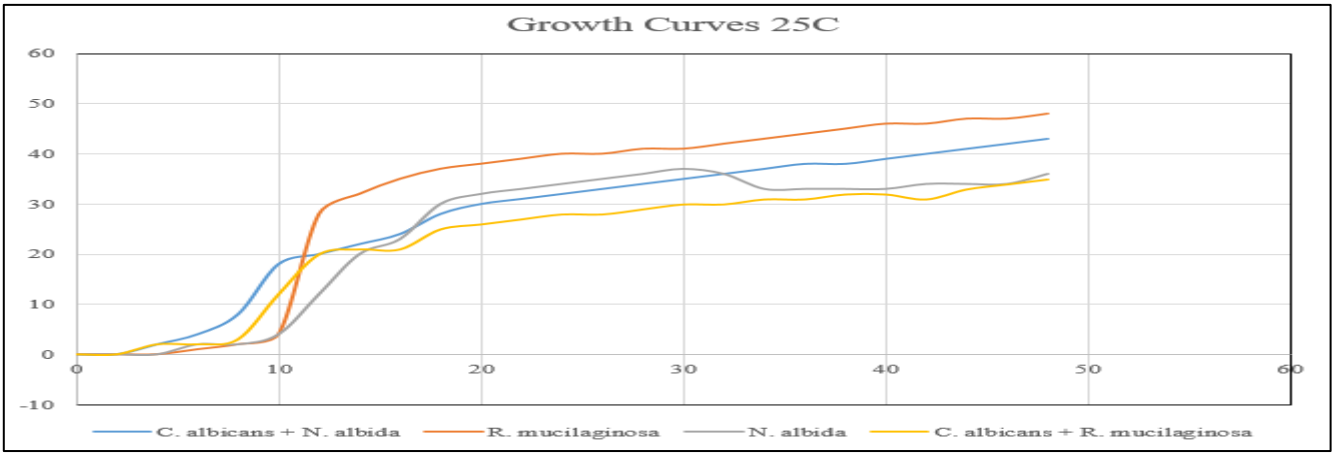
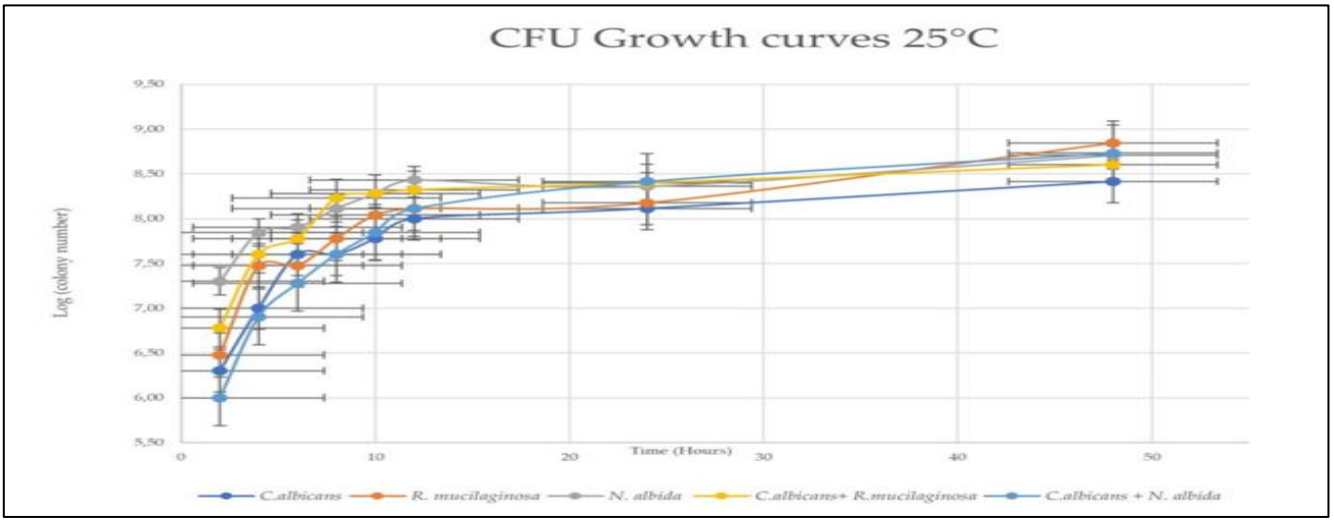
cell membranes of epithelial and endothelial cells less stable, and lipases change how cells talk to each other in their environment.

The development of biofilm is a key factor in virulence.It all starts when C. albicans cells stick to the outside of a foreign object, making a layer of cells and increasing the production of hyphal wall proteins (Pokhrel, et al 2022). The biofilm is then kept stable by active cell growth, the production of extracellular matrix, and the formation of hyphae. The Candida biofilm keeps the cells safe from the immune system and medicines that kill fungi. The hyphal-associated peptide poison candidalysin Ece1 that C. albicans makes is also an important virulence factor that is needed to cause infections in the lining of the mouth and throughout the body. It has been known for a long time that candidalysin is a hemolytic factor of C. albicans that helps the yeast get nutrients it needs to live and reproduce (Mogavero, et al 2022). Additionally, candidalysin is a key part of initiating innate antifungal defense during infection, which depends on neutrophil and interleukin 17 (IL-17) responses. It's important to know that candidalysin can indirectly turn on the epidermal growth factor receptor (EGFR). This is done through a complicated process involving EGFR and matrix metalloproteinase (MMP) ligands, both of which play a role in many types of cancer.

Changes in phenotype help C. albicans get used to its surroundings (in this case, the host tissue). It is possible for C. albicans to destroy the protective layer of the host epithelium, cause apoptosis or necrosis, and then change the structure of the epithelial cell (Lapaquette, et al 2022). This hurts the epithelial cells and changes the usual structure, which causes abnormal cell growth that is linked to cancer. Also, Candida's ability to make biofilms can expose host tissues to fungal carcinogens like acetaldehyde for a long time and cause more hydrolases to be made, which can weaken the innate immune system and cause chronic inflammation. Chronic inflammation from microbial diseases is one of the things that can make you more likely to get cancer.



(A)



(B)

Fig 2: (A) Graphical representation of the optical density OD (600 nm) vs. Time (hours) of the 48-h growth curve of the strains *C. albicans*, *R. mucilaginosa*, and *N. albida* and the mixtures of the two last yeasts with *C. albicans*;
(B) Graphical representation of the log (CFU/mL) vs. Time (in hours) of the growth curve of the three yeasts isolated and the mixtures of *C. albicans* + *R. mucilaginosa* and *C. albicans* + *N. albida*.
Source: Caetano, et al 2023

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Hence it is possible for infections and long-term colonization of the mucosal epithelium to lead to a chronic inflammatory disease (Zhang, et al 2022). According to Zhang et al. (2022) (Table 3), C. albicans can recognize Toll-like receptors (TLRs) and C-type lectin-like receptors (CLRs). These then trigger the corresponding MAPK (Mitogen-Activated Protein Kinase) and NF-κB (Nuclear Factor Kappa B). In particular, the inflammatory signaling system and interferon make many inflammatory genes more active. They are necessary for both cancer and benign conditions to grow. Specifically, cyclooxygenase enzymes (COX), MMPs, and prostaglandins can stop tumor suppressor genes from working by changing DNA methylation and post-translational modifications. This could lead to the growth of cancer.

III. RESULTS AND DISCUSSION

A. The Role of Candida in Oral Malignancy

Planocellular carcinoma, also called oral squamous cell carcinoma, makes up more than 90% of oral cancers and is the most common type of cancer found in the mouth (Inchingolo, et al. 2020). It can happen in many places in the mouth, like the tongue, lips, gums, palate, or buccal tissue. It is more than half the time that oral planocellular carcinoma starts from precancerous tumors that show up as white or red spots on the mucosa (leukoplakia/erythroplakia). Unfortunately, the outlook and survival numbers after five years are not very good, and 50% of cases end in death.

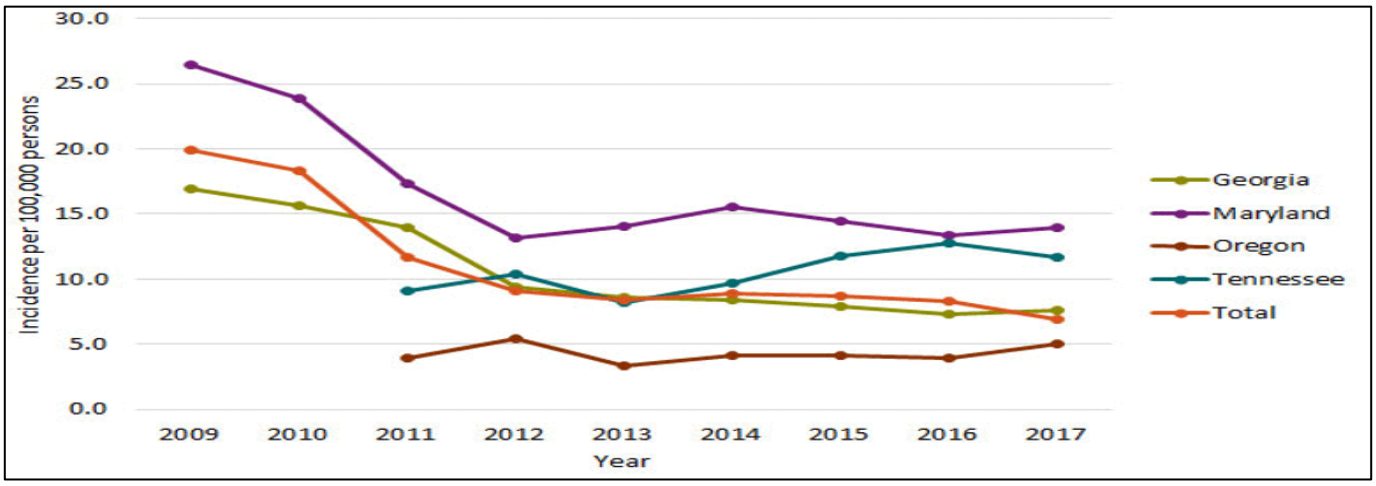

Fig 3: The Incidence and Prevalence of Candida

People have been talking about the link between Candida spp. and mouth cancer for a long time. Different ways this genus of fungi might be connected to the growth of oral cancer have been mentioned (Sultan, et al 2022). Some of the ideas behind this are that it causes genetic instability in mouth cells, helps epithelial cells change, produces cancer-causing substances, changes the immune system, and causes chronic inflammation (Yu, et al 2022). A recent systematic review found that having a specific species of the genus, C. albicans, in the mouth could be connected to the development of oral cancer. This is because it changes the phenotypic structure of cells and also changes their genotype (Ayuningtyas, et al 2022). It was also stressed that C. albicans makes substances that can cause cancer and help oral cancer spread.

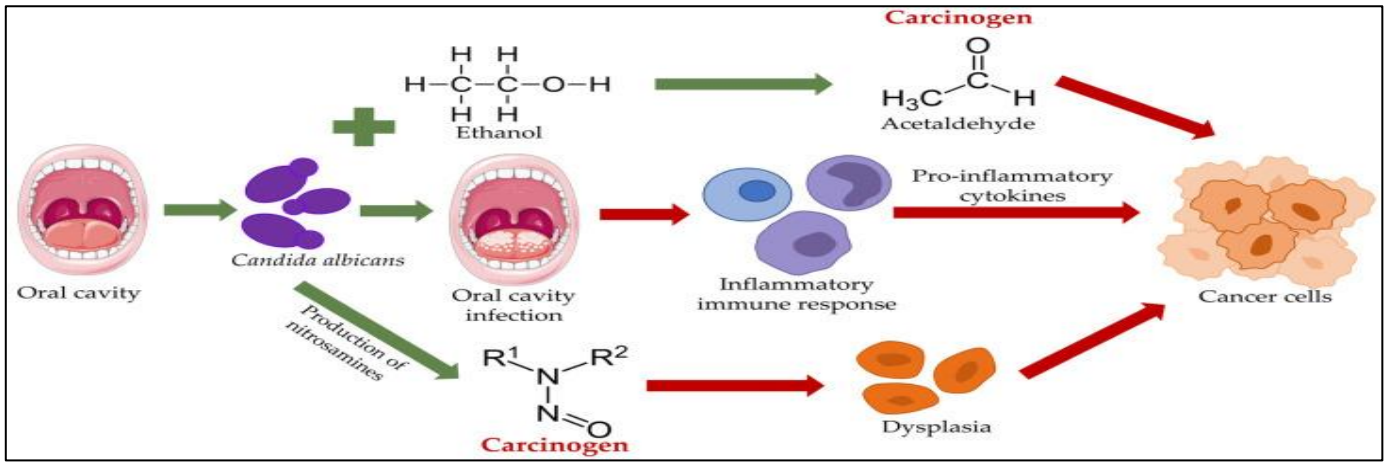

Fig 4: An Overview of the Various Pathways by which Candida Albicans May Contribute to the Development of Oral Cancer

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Researchers contend that C. albicans can directly cause mouth cancer by making cancer-causing enzymes and other chemicals that can damage DNA and help cancer cells grow and stay alive. Nitrosamines and acetaldehyde are two substances that belong to this group (Krogh, et al. 1998). This ability of oral Candida to turn alcohol into acetaldehyde has been shown to be very important. Acetaldehyde is known to break DNA and stop DNA repair systems from working. This can cause genetic mutations and chromosomal problems that are linked to cancer growth. This substance also links indirectly to glutathione, an important antioxidant. This makes reactive oxygen species more common, which leads to chronic inflammation and damage to mitochondria (Manzo-Avalos, et al. 2010). Infection with C. albicans can also weaken the immune system, which makes the person more likely to get cancer. Lastly, this fungus can stop apoptosis, which is also known as planned cell death. This process normally gets rid of damaged or abnormal cells in the body, but this fungus can stop it, letting them keep multiplying and possibly turning into cancer.

This fits with what we've learned recently. A study from Hungary showed that C. albicans increases the growth, migration, and invasion of oral squamous cell carcinoma cells in the lab. It also increases tumor growth and spread in animals. These researchers found that when C. albicans infects cancer cells, it increases gene expression related to controlling the cell cycle, inflammatory processes, and the change from epithelium to mesenchymal cells. These results suggest that C. albicans may help oral squamous cell carcinoma spread, both in its early and late stages. It does this by changing the way tumor cells behave and the immune system's response to them. It does this by increasing oncogenes and making a premalignant phenotype stronger, which has important clinical implications (Vadovics, et al 2022).

Wang et al. wanted to look into how C. albicans causes mouth cancer from the point of view of the immune microenvironment around the tumor. In cases of C. albicans infection, they determined that both IL-17A and its receptor (IL-17RA) increased in levels for macrophages and cells affected by mouth cancer. This could also mean that increased signaling of IL-17A/IL-17RA actively, in turn, switches on the macrophages to encourage the release of inflammatory cytokines, which then allows the growth, migration, and invasiveness of oral cancer cells (Talapko et al., 2023). It was also reflected that IL-17A/IL-17RA signaling due to C. albicans serves its function in the xenograft growth of mouth cancer in living organisms.

There is more proof that these two things are linked. Using single-cell expression profiling, Hsieh et al. discovered that immune cells can be seen infiltrating cancer cells caused by a C. albicans infection and figured out the full mechanisms that make these processes possible.

Wang and his colleagues found that C. albicans raises the level of programmed death-ligand 1 (PD-L1) in oral cancer cells both in the lab and in living organisms. This stops T cells from activating and multiplying. Another study by Marin-Dett et al. (2023) discovered that a C. albicans biofilm may help mouth cancer grow and spread by creating lipid droplets and making chemotherapy drugs less effective. At this point, there aren't any solid conclusions, but there is more and more evidence that this species of Candida is linked to a higher chance of developing oral squamous cell carcinoma.

Table 6: Mechanisms of C. albicans-Induced Oral Cancer Progression and Immune Evasion

No.	Mechanism	Data 1	Data 2
1	Increases cancer cell growth/migration/invasion		
	- Tumor volume in mouse model (mm^3)	350-400	250-300
	- Invasion of oral cancer cells (%)	25-30%	20-25%
2	Changes gene expression		
	- Fold increase in oncogene expression	2-3x	1.5-2x
	- Decrease in E-cadherin mRNA (%)	50-60%	40-50%
3	Activates macrophages through IL-17A/IL-17RA		
	- IL-17A levels in tumor (pg/mL)	150-200	100-150
	- IL-17RA+ macrophage %	30-40%	25-35%
4	Increases PD-L1 levels		
	- PD-L1 expression on cancer cells	2-3x	1.5-2x
	- Reduction in CD8+ T cells (%)	50-60%	40-50%
5	Enhances chemoresistance		
	- Tumor viability with fluconazole (%)	80-90%	70-80%
	- Lipid droplet accumulation	15-20 droplets/HPF	10-15 droplets/HPF

This is another important virulence factor that may have something to do with how C. albicans affects the growth of mouth cancer. It is a protein toxin that releases the fungus C. albicans. This fungus is known for causing oral candidiasis, a common fungal illness found in the mouth. The complete contribution of candida lysin to cancer development in the oral cavity has yet to be identified. However, some works discovered that the peptide might play a main role in the cancer initiation process in this organ (Findley et al., 2013). The authors observed that candidalysin stimulates and activates the immune system by giving it a defense response in the form of inflammation that may lead to further cancerous growth. A similar finding was also observed with ORF, in which candida lysin was seen to cause damage to the

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cellular membranes of oral epithelial cells, giving rise to DNA damage and mutations. In addition, candidalysin induced angiogenesis and new blood vessel formation. Angiogenesis is one of the most important factors in the growth of cancer and metastasis to several tissues and organs from the primary tumor. This signifies that candida lysin could enhance the progression of oral carcinoma. In other words, further research is needed to understand fully what this molecule takes in terms of oral carcinoma. This is a necessary condition for the development and progression of this disease.

It's important to note that C. albicans usually lives in people's mouths. It is the most common yeast fungus on skin that is healthy and skin that is sick (Talapko et al 2021). That's why more research is needed to fully figure out the link in the process of how cancer starts. Changes in homeostasis, which can be caused by genetic and environmental factors that may be local or widespread, are what turn it into a pathogenic state and cause opportunistic infections.

C. albicans infections in the mouth are common in cancer patients who are receiving chemotherapy or radiotherapy. These infections are caused by an opportunistic pathogen that takes advantage of the state of immunosuppression and are generally linked to malignancies. Along with the studies that were already done, however, its part in starting and spreading oral cancer has recently been studied more (Huët, et al 2022).

There are many different types of candidiasis because of the wide range of symptoms that can come from C. albicans infections in the mouth. The change in color in the mouth can be broken down into red and white, as well as main and secondary, based on where it comes from. When you have primary candidiasis, you only have illnesses in your mouth and around your gums. But when the infection happens because of a systemic disease and the mucous is already changed (making it easier for the infection to spread), this is called secondary candidiasis. The main types of the disease are pseudomembranous candidiasis, acute erythematous candidiasis, chronic erythematous candidiasis, and chronic hyperplastic or nodular candidiasis. Angular cheilitis, medial rhomboid glossitis, and chronic mucocutaneous candidiasis, on the other hand, are secondary (Hellstein, et al. 2019).

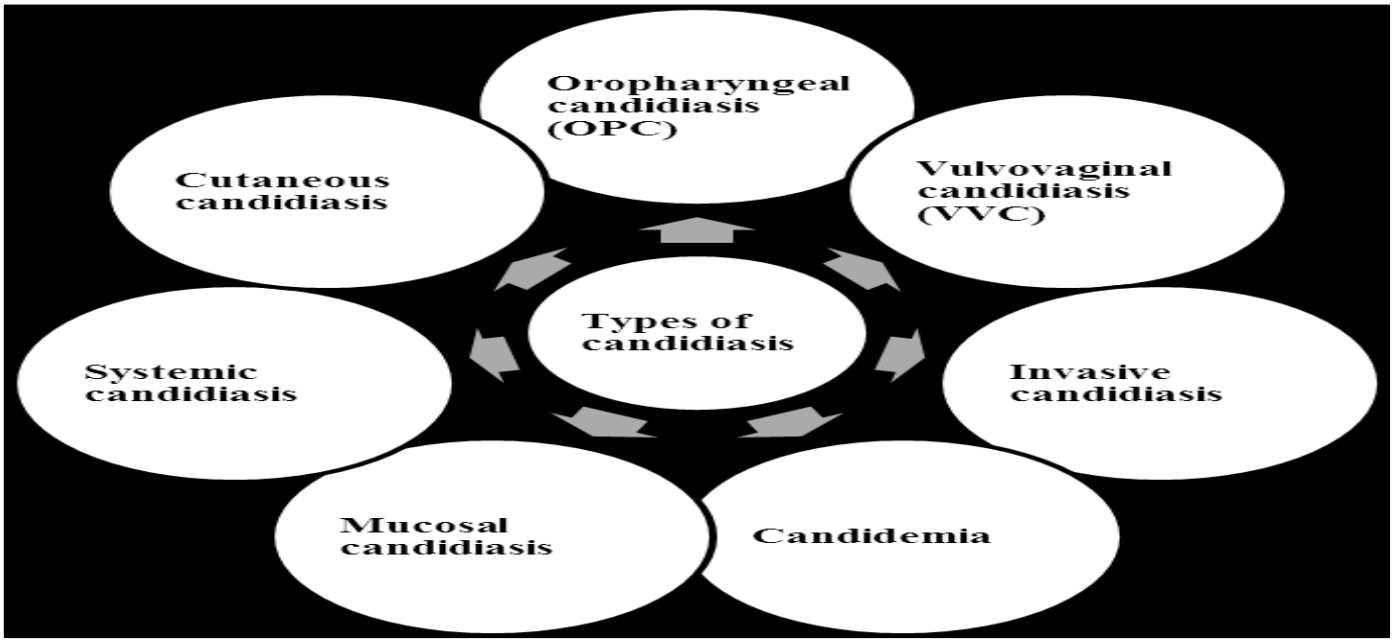

Fig 5: Major Types of Candidiasis
Source: Meora, et al (2015)

Chronic hyperplastic candidiasis, which is also called Candida leukoplakia, has the highest chance of turning into cancer of all the oral lesions caused by Candida. It is marked by white crystals on the mucous membrane that are hard to get rid of even with gentle scraping. This makes it different from other kinds of candidiasis and sores that also look like white deposits. The reason for this is that fungus hyphae get deep into the tissues of the mouth. White deposits in the mouth can be homogeneous or heterogeneous. Heterogeneous deposits are more likely to change into cancerous ones. Oral tissue changes don't hurt most of the time, but they might hurt when touched, when spicy foods are eaten, or when it gets hot. They can happen anywhere in the mouth, but most often on the sides, under the tongue, and on the inside of the cheeks (Hellstein, et al. 2019). The exact cause of oral leukoplakia is unknown, but it is thought to be linked to mouth tissues being irritated over time, like when you smoke, have rough teeth, or use dental appliances. Oral leukoplakia is generally treated by getting rid of the thing that is irritating it, like quitting smoking or getting new dental appliances that don't fit right, and keeping an eye on the patches to see if they change or grow over time. In some cases, a biopsy may be needed to find out if the spots are cancerous or showing signs of becoming cancerous.

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Some people think that a Candida illness can help cause cancer when other risk factors are present. One example is people who smoke or drink too much. A Candida infection may work together with these habits to make getting mouth precancerous lesions more likely (Ayuningtyas, et al 2022). It's not completely clear how important C. albicans is in the development of oral cancer, but there is some proof that it may play a part. It has also been evidenced that an overdose of C. albicans will further cause chronic inflammation among its many causes, even leading to a predisposition to oral cancer. This may also result from the interaction of Candida with other species of oral microorganisms in the occurrence of certain oral diseases. Candida, for instance, has also been found to be associated with bacteria such as Streptococcus mutans, one associated with cavities in teeth, and Porphyromonas gingivalis, which is associated with the onset of gum disease. The above process of interactions will lead to the formation of mixed-species biofilms that result in higher potentials of these microorganisms to become more virulent and ultimately give rise to serious oral diseases like oral premalignancy and malignancy.

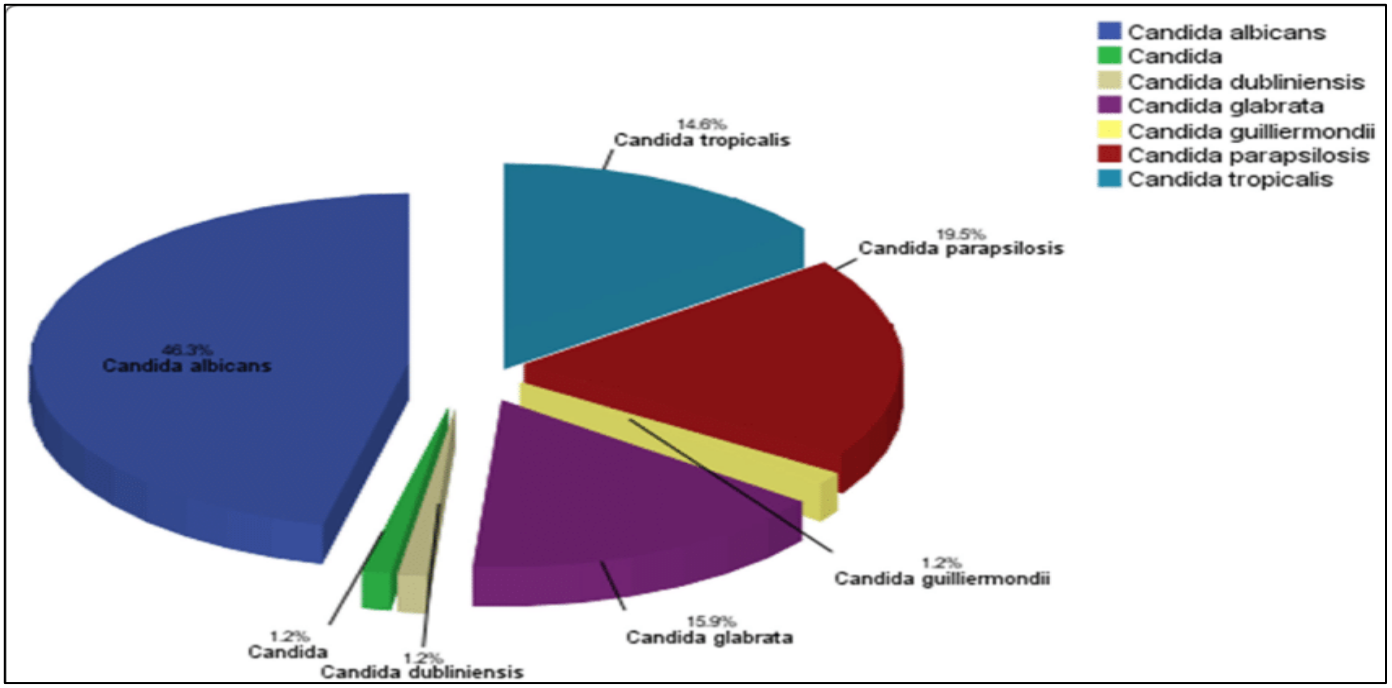

Fig 6: Distribution of Candida Species Responsible for Candidiasis (n = 82). Candida albicans (n = 38), Candida parapsilosis (n = 16), Candida glabrata (n = 13), Candida tropicalis (n = 12), Candida dubliniensis (n = 1), Candida guilliermondii (n = 1), Candida spp. (n = 1).
Source: Xiao, et al (2019)

Patients with chronic or recurrent Candida infections generally have an increased chance of oral cavity cancer, particularly in those whose immune competency is altered, either due to immunosuppression or to other risk factors for oral cavity cancer. Keeping your mouth microbiome healthy by brushing your teeth and going to the dentist regularly can help stop these conditions from happening. For these people, it's important to see a doctor right away if they have oral signs like sores or white patches, and to treat the underlying risk factors to keep oral cancer from happening.

B. Possible Preventive Measures and Treatment.

Some name it candidiasis or thrush. Candidiasis is caused by any Candida yeast. More than 20 candida species can cause illness, however Candida albicans is the most prevalent (Kabir & Ahmad, 2013). Candida infections can range from minor to life-threatening. Topically applied antifungals cure skin, mouth, throat, and genital infections. Systemic candidemia can result from candidiasis spreading throughout the body in weak immune systems. Untreated invasive candidiasis can kill 40% of patients, even with antifungals (Kabir & Ahmad, 2013). Since candidiasis is becoming more widespread worldwide, prevention is crucial. Correctly diagnosing and treating infections improves results. This section covers all the approaches to prevent and cure candidiasis based on the current clinical research and guidelines.

C. Prevention Strategies

➢ *Screening and Pre-emptive Treatment*

Invasive candidiasis is more common in long-term ICU patients, parenteral nutrition, broad-spectrum antibacterial medications, hematologic malignancy, and hematopoietic stem cell transplantation (Kaufman, 2003). These critically ill or immune-compromised patients can be tested for intestinal Candida infection to determine if they need antifungal treatment (Kaufman, 2003; Kabir & Ahmad, 2013). To check for Candida and take fluconazole as a preventative step, you are less likely to have invasive candidiasis than if you only took it for screening cultures (Kaufman, 2003). When high-risk surgery ICU patients established Candida during weekly

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screening, echinocandin prophylaxis was associated with reduced incidence of invasive candidiasis than fluconazole or sugar pills (Kabir & Ahmad, 2013). Screening and prevention can reduce infections in high-risk groups, therefore consider them when money allows.

➢ *Hand Hygiene and Environmental Disinfection*

Washing your hands often is the best way to stop healthcare-associated illnesses, like candidiasis, from spreading. Employees and guests of healthcare facilities must wash their hands properly with soap and water or an alcohol-based hand sanitizer, especially before and after touching high-risk patients (Kabir & Ahmad, 2013). Frequent disinfection of surfaces and tools near high-risk patients lowers the fungal bioburden and the chance of cross-contamination. The task must be carried out using an EPA-approved disinfectant that says on the package that it kills fungi and spores (Ahmad & Alfouzan, 2021). For multidrug-resistant Candida auris breakouts, strict cleaning and disinfecting rules must be followed along with wearing gowns and gloves when touching patients. Consistently following infection control measures requires ongoing training and feedback on performance (Ahmad & Alfouzan, 2021). To stop outbreaks and lower the number of invasive fungal diseases in healthcare settings, strict adherence to these steps is needed.

➢ *Antibiotic Stewardship*

Indiscriminate use of broad-spectrum antibacterial drugs upsets the normal microbiota and allows Candida to flourish. A retrospective study found receipt of antibiotics, notably fluoroquinolones, was an independent risk factor for invasive candidiasis in the ICU (Kabir & Ahmad, 2013). Antibiotic stewardship programs that promote optimized treatment selection, dosing, route and duration can minimize disruption of protective microbiota (Kaufman, 2003). This strategy has been shown to lower rates of Clostridium difficile and antimicrobial resistance, and may also reduce invasive candidiasis incidence over time.

➢ *Control of Predisposing Conditions*

Candidasis is more likely to happen in people with diabetes, HIV/AIDS, and intravenous devices. People with diabetes who strictly control their blood sugar, people with HIV who take antiretroviral drugs, and people who follow aseptic procedures for placing and maintaining tubes make it less likely for Candida to get into tissues (Kaufman, 2003; Pappas et al., 2004). Treating any underlying cancer, keeping up with diet, and reducing immunosuppression as much as possible also makes patients less likely to get opportunistic Candida infections.

➢ *Patient Education*

Community-acquired mucosal candidiasis can be lowered by making simple changes to your lifestyle, as suggested by your doctor. Keeping your mouth clean by cleaning and brushing your teeth after every meal can help control oropharyngeal candidiasis (Kabir & Ahmad, 2013; Pappas et al., 2004). Vulvovaginal candidiasis can't happen again if you teach people good genital cleanliness and how to use birth control correctly (Kabir & Ahmad, 2013). This means that educating patients is an important part of primary protection.

➢ *Treatment Approaches*

Prompt diagnosis and initiation of appropriate antifungal therapy is important for favorable outcomes in candidiasis. The Infectious Diseases Society of America provides treatment guidelines for systemic fungal infections based on available evidence (Pappas et al., 2004).

➢ *Topical Antifungal Agents*

Topical antifungals work well for most cases of superficial mucocutaneous candidiasis because they reach high effective tissue levels with few side effects and systemic absorption. Azoles, such as clotrimazole, miconazole, or nystatin, are often used for 7–14 days to treat oral and genital diseases (Pappas et al., 2004). For a clinical cure, there needs to be enough contact time and multiple treatments. Aside from oral medicines, topicals can also be used to treat invasive candidiasis that affects the skin or pharynx.

➢ *Systemic Antifungal Therapy*

For non-neutropenic individuals with mild to moderate invasive candidiasis such esophageal candidiasis, systemic fluconazole is the primary choice since it works well and is safe (Pappas et al., 2004). Some studies demonstrate that echinocandins treat invasive candidiasis better than fluconazole because they don't combine with other medications and kill fluconazole-resistant Candida species (Kabir & Ahmad, 2013). Caspofungin, micafungin, and anidulafungin are appropriate first-line treatments for moderate to serious infections or critically ill patients. They destroy Candida and are better tolerated than amphotericin B (Pappas et al., 2004). Empiric echinocandin therapy is suggested above other medications for the first treatment of potential invasive candidiasis in neutropenic or azole antifungal-exposed patients (Pappas et al., 2004).

Oral fluconazole can be used if echinocandin works (Pappas et al., 2004). For uncomplicated cases, treatment takes two weeks. It takes 6-8 weeks for endocarditis, osteomyelitis, and meningitis (Kaufman, 2003; Pappas et al., 2004). For recurring infections, suppressive treatment can be lifelong. Amphotericin B is hazardous and used exclusively as a second-line treatment or in resource-poor areas. Liposomal amphotericin B is easier for the body to absorb than deoxycholate (Kaufman, 2003; Pappas et al., 2004). It is still a possibility for intolerant, allergic, or refractory patients who have exhausted other choices. In addition to antifungals, therapy should address underlying problems, drain abscesses or remove infected devices, and treat sepsis. Monitoring the patient's reaction and repeating susceptibility testing can help doctors decide whether to increase, decrease, or mix therapy.

➢ *Refractory Invasive Candidiasis*

Some invasive candidiasis patients may not respond to the first treatment. Combination antifungal treatment may improve these infections, however there is little proof (Pappas et al., 2004). A randomized investigation of Candida endocarditis found that lipid amphotericin B with flucytosine was more effective than amphotericin B alone (Kabir &

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Ahmad, 2013). Case series have shown inconsistent results for echinocandin-fluconazole, amphotericin B-flucytosine, and others (Pappas et al., 2004). It works best for non-albicans Candida species infections that are harder to treat or long-term infections like endocarditis. Use combinations sparingly since they may be more hazardous and expensive than high-dose monotherapy.

IV. CONCLUSION

In conclusion, C. albicans' cancer link is expanding. However, this analysis indicates several ways long-term candidal infections may increase cancer risk and growth. Scientists observed that C. albicans can alter its host's immune system and microbiome, which may help cancer spread. Ethanol and acetaldehyde, genotoxic substances, can directly damage epithelial cells and modify DNA during protracted colonization. More research with good prospective designs are needed to corroborate these processes and indicate C. albicans causes some cancers. In cancer-prone locations, stopping chronic candidiasis may reduce cancer risk if a cause-and-effect link can be proven. Early detection and effective antifungal treatment can reduce the "fertile field effect" by reducing fungus and their spread. Combination therapy with anti-efflux pump inhibitors may help fight azole resistance. After finding safe and effective options, monoclonal antibodies or vaccinations may help control Candida for a long period. A multifaceted treatment that combines antifungals and supportive care may break the C. albicans-cancer connection.
Researchers know nothing about the complex host-pathogen interactions that may alter this process. Mycology, microbiome science, and onco-immunology research is needed to understand opportunistic fungus like C. albicans. Bigger prospective cohort studies will validate early findings and assist establish evidence-based cancer screening and candidiasis treatment guidelines. Researchers should continue studying this topic since it may lead to new clinical insights and Candida-related cancer treatments.

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