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### An overview on invasive Candidiasis capable of causing cancer in human

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#### Abstract

For the past several years, we are familiar with the bacterial and viral origin of cancers, so it may not be so far fetched to stretch causation to fungal overgrowth. It appears that the number of patients with fungal overgrowths has risen dramatically with compromised immune responses in the last half century (David *et al.* 2015). Dr. Johannes Fibiger, a Nobel laureate of Denmark in 1913 had already proved the fungal connection with the development of cancer in human by feeding rats with parasitic larval-carrying cockroaches infected by fungi. These rats developed cancer (Fibiger 1913). Fungi have, thus, also been found to cause a variety of cancers especially the cancer developed by the *Candida albicans*. The present paper deals with the study of invasive Candidiasis causing cancer in the light of recent researches done so far in the field of microbial origin of cancer.

**Keywords:** Candidiasis, *Candida albicans*, cancer

#### 1. Introduction

In 1913, a Nobel laureate, Dr. Johannes Fibiger of Denmark proved the fungal connection with cancer by feeding rats with parasitic larvae-carrying cockroaches infected by fungi. These rats develop cancer (Fibiger 1913) [1]. Since then the researches have been carried on to evaluate a number of fungi capable of causing cancer. There is currently an increasing concern about the opportunistic fungus *Candida albicans* that increases the risk of carcinogenesis and metastasis. The genus *Candida* with their species *albicans* were for the first time described by a botanist named Christine Marie Berkhout in her doctoral thesis at the University of Utrecht in 1923. The species has also been known in the past as *Monilia albicans* and *Oidium albicans* giving white appearance when cultured (Berman and Sudbery 2002) [3]. This fungus persists in our body lifelong in an ecofriendly manner but when its growth are forcibly disturbed due to some unavoidable circumstances such as misuse of antibiotics, use of diets high in sugary foods, beverages containing high caffeine, excess alcohols, cigarette smoking and a long period of anxiety or worry, their growth is enhanced. (Harpe 2004 and Masroor *et al.* 2016) [16, 28]. Since, our body is in state of ecobalance it can only tolerate a certain amount of disturbances. Therefore, when this goes out of balance, the same ecofriendly microorganisms are turned out to be pathogenic causing certain ailments, diseases and even cancer in certain parts of the human body (Tortorano *et al.* 2006, Norgaard *et al.* 2013, Schwabe and Jobin 2013, Guinea 2014, Martins *et al.* 2014, Wang *et al.* 2014, Erdogan and Rao 2015, and Hidalgo and Vazquez 2015) [10, 15, 17, 26, 36, 51, 56, 61].

Candidiasis or Candidosis is a fungal infection caused by *Candida albicans*. According to British english the term "Candidosis", while in American english the term "Candidiasis" are largely used. It mostly affects the openings of the body like mouth and vagina. When it affects the mouth, it is called as "thrush". Currently, it has been clamied that one-third human population of the world have been affected by *Candida*, a condition known as Candidiasis hypersensitivity (Odds 1987, Nolting *et al.* 1994, Schiefer 1997, Akpan and Morgan 2002, Tortorano *et al.* 2006, Pfaller and Diekema 2007, Perlroth *et al.* 2007, Lim *et al.* 2011, Calderone and Clancy 2012, Nyirjesy and Sobel 2013, Guinea 2014, Martins *et al.* 2014, Hidalgo and Vazquez 2015, Patil *et al.* 2015 and Pappas *et al.* 2016) [2, 5, 15, 17, 23, 26, 35, 37, 38, 41, 42, 43, 44, 50, 56]. The present piece of research work highlighted Candidiasis caused by the *Candida albicans* developing cancer in human.

## 2. Methodology

The present paper is prepared on the basis of researches done so far in the field of microbial origin of cancer. Several research papers were consulted in order to explore the various theories put forward to explain that how the *Candida albicans* causes cancer in the human body. The paper is an attempt to summarize the current knowledge in the light of recent researches available so far in the same field.

## 3. Results and Discussion

Several types of Candidiasis have been reported so far as **Mucosal Candidiasis** i.e., Oral Candidiasis causing oral thrush, Oropharyngeal and Esopharyngeal Candidiasis, Gastrointestinal Candidiasis, Pseudomembranous Candidiasis, Erythematous Candidiasis, Hyperplastic Candidiasis, Candidal vulvovaginitis, Candidal balanitis and Respiratory Candidiasis (Akpan and Morgan 2002, Kontoyiannis *et al.* 2000, Yamada and Alpers 2009, Nyirjesy and Sobel 2013, Martins *et al.* 2014, Wang *et al.* 2014, Erdogan and Rao 2015, Hidalgo and Vazquez 2015 and Patil *et al.* 2015) [2, 10, 17, 20, 26, 37, 42, 61, 63]; Cutaneous Candidiasis i.e., Congenital Cutaneous Candidiasis, Chronic Mucocutaneous Candidiasis, Candidal folliculitis, Candidal intertrigo, Candidal onychomycosis, Candidal paronychia, Perianal Candidiasis and Diper Candidiasis (Nolting *et al.* 1994 and Hidalgo and Vazquez 2015) [17, 35]; Systemic Candidiasis i.e., Candidemia, Invasive Candidiasis and Chronic Systemic Candidiasis (Hidalgo and Vazquez 2015) [17] and Antibiotics Candidiasis (Harpe 2004) [16].

Further, the risk factors for invasive Candidiasis include being in an intensive care unit following surgery, low birth weight infants and those with weak immune system (Leleu *et al.* 2002 and Pappas *et al.* 2016) [22, 41]. Sometimes, diabetes, use of oral contraceptives, pregnancy and indiscriminate use of hormones and antibiotics have also been found to be reported as risk factors (Schiefer 1997, Harpe 2004, Pfaller & Diekema 2007 and Nyirjesy and Sobel 2013) [16, 37, 44, 50].

Many scientists believe that cancer really begins with fungal infections. Research shows that fungal overgrowth may be in the root cause of cancer. The most common in human pathogenic fungi are the *Candida* and species-in particular the *Candida albicans*. This is a fungus that lives in the human body without any noted harm. This is generally found in the mucosa of digestive tract, oral cavity and vagina. It causes an overgrowth in the digestive tract and may cause burning in stomach, especially after eating something sweet or vinegary in food. Lethargyness, brain fog, mood swings, little bumps on the roof of mouth, a coated tongue with a few unsavory things and vaginal yeast infections are some of the symptoms of *C. albicans* infection (Krogh 1990, Schiefer 1997, Phan *et al.* 2000, Akpan and Morgan 2002, Simoncini 2005, Meurman and Uittamo 2008, Yamada and Alpers 2009, Mohd Bakri *et al.* 2011, Sanjaya *et al.* 2011, Norgaard *et al.* 2013, Ramirez-Garcia *et al.* 2014 & 2016, Wang *et al.* 2014, Erdogan and Rao 2015 and Patil *et al.* 2015) [2, 10, 21, 30, 31, 36, 42, 45, 46, 47, 49, 50, 53, 61, 63].

Oral mucosal disorders due to the overgrowth of *Candida albicans* in mouth and vagina have extensively been studied in connection with the development of cancer (Williamson 1969, Hurley and Louvois 1979, Krogh 1990, Ogrady and Reade 1992, Akpan and Morgan 2002, Sobel 2007, Meurman and Uittamo 2008, Dalle *et al.* 2010, Mohd Bakri *et al.* 2010, Zhu and Filler 2010, Sanjaya *et al.* 2011, Villar *et al.* 2012, Gainza-Cirauque *et al.* 2013, Nyirjesy and Sobel 2013 and Patil *et al.* 2015) [2, 6, 14, 19, 21, 30, 31, 37, 39, 42, 49, 54, 59, 62, 66]. The

thrush, if left unchecked it causes erosions and ulcerations in the tissues of pharynx and oesophagus creating, sometimes, chest pain and difficulty in swallowing. Similarly, if left further for a longer period of time death may occur as a result of sepsis. Nearly, seventy per cent deaths occur in cases of disseminated Candidiasis. In extreme cases it may enter into the bloodstream causing sepsis and disseminated Candidiasis to other organs like CNS, kidneys, liver, bones, muscles, joints, spleen and eyes (Zirkel *et al.* 2012) [67]. Although, Candidal sepsis is rare but, Candidal overgrowth usually causes Leaky Gut Syndrome (LGS) where hyperpermeability occurs due to the damage of intestinal wall. It allows some undesirable substances to enter in such a way that body derecognizes and accept it as a foreign body and forms antibodies against it. The body becomes allergic for those substances they would previously been able to eat without any problem. This is a kind of immunity failure resulting in the damage of certain organs of the body associated with them (Harpe 2004) [16]. Some scientists also implicate *Candida* as a cause of leukemia (Aisha and Saba 2005 and Olga *et al.* 2016) [1, 40].

Several scientists have hypothesized the Candidal origin of cancer and they have documented the co-existence of cancer with Candidiasis (Diller and Fisher 1950, Thomas *et al.* 1996, Mohd Bakri *et al.* 2010, Sanjaya *et al.* 2011, Norgaard *et al.* 2013 and Ramirez Garcia 2014 & 2016) [9, 31, 46, 47, 49, 55]. An Italian oncologist Dr. Tullio Simoncini in his book entitled "Cancer is a fungus" described a link between cancer and *Candida*. According to him cancer is caused by an yeast named *Candida albicans*. And, this hypothesis is based on the affinities found similar in both of them as they feed, grow and reproduce anaerobically in an acidic environment on sugar appearing white in colour and uneven in texture. Simoncini believes that *Candida* produces cancer and this is not usually a consequence of cancer that comes lateron. And he found *Candida* in almost every cancerous tumours. Here, not only the metastatic human cancerous cells but in disseminated Candidiasis, the transformed Candidal cells capable of causing cancer have doubled the possibilities of developing cancer in different parts of the body (Diller and Fisher 1950 and Simoncini 2005) [9, 55].

Rise in the rate of cancer has been correlated with the carbohydrate-rich and fiber-weak diets comprising of processed white sugar, refined wheat and other foods with high glycemic counts promoting the growth of *Candida albicans*. It disrupted the number of good and bad bacteria within the body causing to lower the immune responses, slowed wound healing and cancer. The fungi causing cancer is similar in the series to bacteria and virus as *Helicobacter pylori* and Human Papilloma virus which have already been reported to develop gastric and cervical cancer respectively (Zur Hausen 2002 & 2010, Shanks and El-Omar 2009 and de Sanjose *et al.* 2010) [8, 52, 68, 69]. Similarly, indiscriminate use of antibiotics perishes the probiotic good bacteria leading to chronic Candidiasis causing cancer in future (Harpe 2014) [16]. In an immunocompromised patient due to the blocking of immune responses these *Candida* cells multiplied and flourishes in such a way that it sets mutated and adapted freely to cause cancer. Further, Is there any link between *Candida* and breast cancer ? A large percentage of women diagnosed with breast cancer were having an overgrowth of *Candida albicans* (Magnus Gottfredsson *et al.* 2003) [25].

*Candida albicans*, in general is the most common cause of hospital acquired infections producing not only superficial infections as oral and vaginal Candidiasis, but life threatening

systemic infections too (Pfaller and Diekema 2007, Perlroth *et al.* 2007, Calderone and Clancy 2012 and Zirkel *et al.* 2012) [5, 43, 44, 67]. The ability of *C. albicans* to infect such diverse host niches to cause pathogenicity and cancer has always been supported by a wide range of fitness attributes and virulence factors. Fitness attributes include rapid adaptation to fluctuations in environmental pH, metabolic flexibility, powerful nutrients acquisition systems and robust stress response mechanisms (Krogh 1990, Rotstein *et al.* 2000, Lorenz and Fink 2001, Verstrepen and Klis 2006, Brand *et al.* 2007, Zakikhany *et al.* 2007, Zhao *et al.* 2007, Naglik *et al.* 2003 & 2011, Nicholls *et al.* 2011, Mayer *et al.* 2012, Villar *et al.* 2012, Wachtler *et al.* 2012, François *et al.* 2013 and David *et al.* 2015) [4, 7, 13, 21, 24, 29, 32, 33, 34, 48, 58, 59, 60, 64, 65].

Some metabolic and genetical changes occur for the full virulence of the pathogen *Candida albicans* for example, activation of the heat shock transcription factor Hsf1, though, small but crucial is essential for stress adaptation and full virulence (Nicholls *et al.* 2011 and Mayer *et al.* 2012) [29, 34]. *Candida albicans* releases integrin like protein and aspartyl proteinases for virulence and pathogenesis (Hostetter 1996 and Naglik *et al.* 2003) [18, 32]. The glyoxylate cycle has been shown to be required for full virulence in *Candida albicans* (Lorenz and Fink 2001) [24]. The production of aldehydes by *Candida albicans* with the use of glucose and alcohol has been reported to cause cancer in human (Krogh 1990, Uittamo *et al.* 2009, Gainza-Cirauque *et al.* 2013 and Marttila *et al.* 2013) [14, 21, 27, 57]. The fungal cells adhere the host cell surfaces by the expression of formation of hyphal growth via thigmotropism (Verstrepen and Klis 2006, Zhao *et al.* 2007, Brand *et al.* 2007) [4, 58, 65]. Lateron, early induction of apoptosis, induced endocytosis and the release of hydrolases facilitated the penetration of hyphae by poking the host wall (Rotstein *et al.* 2000 and Villar *et al.* 2012) [48, 59]. As a result of this function by breaking the barrier very minute holes are formed in the intestinal wall (Rotstein *et al.* 2000, Villar *et al.* 2012, Wachtler *et al.* 2012 and David *et al.* 2015) [7, 48, 59, 60]. The biofilms are also produced for the sake of proper attachment. This is an important virulence factor having capacity to form biofilms on abiotic and biotic surfaces (Verstrepen and Klis 2006 and Finkel and Mitchell 2011) [12, 58]. Finally, with the help of active penetration and endocytosis *C. albicans* established themselves firmly in the host. (Zakikhany *et al.* 2007, Dalle *et al.* 2010, Zhu and Filler 2010, Naglik *et al.* 2011) [6, 33, 64, 66]. The last cue in the whole process is contact sensing. While contact sensing is the switch to hyphal growth, thigmotropism gives the direction of growth on a particular object such as ridges (Brand *et al.* 2007) [4]. It has been observed that the hyphal stage is more invasive than the budding stage (Phan *et al.* 2000, Berman and Sudbery 2002, Brand *et al.* 2007, Wachtler *et al.* 2012) [3, 4, 45, 60]. *C. albicans* is also able to modulate the extracellular pH according to his own requirement. All these features as described above contribute to its remarkable capacity to coexist as a commensal and to prevail as a fungal pathogen in humans (Zakikhany *et al.* 2007, Naglik *et al.* 2011, François *et al.* 2013 and David *et al.* 2015) [7, 13, 33, 64].

#### 4. Conclusion

*Candida* can pose a problem to cause cancer in human with disrupted microflora and weakened immune system. One of the most common Candidal infections in human is the oral thrush. Patients with Candidiasis of the mouth exhibited a significantly increased risk of cancer. It can spread in other parts of the body as well if patient's immune system is not

functioning properly. Usually the overdose of broad spectrum antibiotics, treatment of cancer and severe stresses are known to develop Candidiasis of mouth and vagina. Vulvovaginal Candidiasis is another common Candidal infections found in human females. This is suggestive that any type of gynecologic cancer should must be screened for invasive Candidiasis. Lastly, the paper is an attempt to demonstrate that how Candidal infections can promote the cancer through several plausible mechanisms. For example, *Candida* can produce nitrosamines which are able to produce cancer in human.

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#### 6. Conflict of interest

The authors have declared no conflict of interest. They have approved the final version of the manuscript contributing equally.

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