INTRODUCTION

1. Candidiasis

Candidiasis is a fungal infection caused by *candida* species. The genus *Candida* is comprised of over 200 species. The medically significant *Candida* species include: *Candida albicans*, *Candida (Torulopsis) glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, *Candida kefyr*, *Candida guilliermondii*, *Candida lusitaniae*, *Candida stellatoidea*, and *Candida dubliniensis* [1]. *Candida albicans* is an opportunistic human fungal pathogen that has received an increasing amount of interest in both clinical medicine and fundamental biology. Usually, *C. albicans* is a member of the normal microbial flora colonizing human gastrointestinal and vaginal tracts [2]. In healthy human hosts, it may only cause a range of mild superficial infections [3]. But in immunocompromised patients, life-threatening systemic candidiasis may develop [4,5]. In recent years, candidiasis has become more and more severe due to the rapid global spread of AIDS and the wide use of powerful antibiotics and immune-suppressive therapies during organ transplant or anti-leukemia therapies [6]. To make the situation worse, treatment of candidiasis is difficult due to the limited choices of anti-*C. albicans* drugs. Furthermore, drug-resistant strains have been found all over the world [7-9]. Thus, in order to control this life threatening disease in a better way, it is essential to understand the biological processes of *C. albicans* relevant to infection. Besides its medical significance, *C. albicans* is also an important model for studying some fundamental biological issues. Researchers have been aware of its dynamic genome as well as its unusual sexual cycle [10-12]. More importantly, *C. albicans* has the ability to grow in different morphologies such as yeast, hyphae and pseudohyphae (polymorphism) in
response to different environmental stimuli. All these morphologies have importance in virulence, and proper transitions between them have been shown to be essential for infection and virulence [13]. To control these transitions properly, *C. albicans* uses multiple biological processes, some of which are conserved for morphological transitions in higher eukaryotes. Thus, elucidating the mechanisms underlying *C. albicans* morphological transitions will undoubtedly contribute to a greater appreciation of fungal pathogenesis and virulence as well as the understanding of cell morphogenesis, polarity control and cell-cycle regulation.

1.1 *Candida albicans*

*C. albicans* is a dimorphic fungus that primarily exists and propagates via its blastospore phenotype (also called blastoconidia). Blastospores are characterized by their oval-shapes, mono-nucleated cells and propagation through cellular budding [14]. Upon perception of environmental signals, *C. albicans* is able to transform into one of two filamentous forms: psuedohyphae and hyphae. Elongated, ellipsoidal cells that are attached to one another are referred to as psuedohyphae, while cells that are considered to be true hyphae are characterized by a cylindrical cellular morphology and are separated by perpendicular septal walls. These hyphal forms are comprised of conjoined cells that are divided by septal walls and are not syncytial in composition. Both the psuedohyphal and hyphal morphologies are routinely referred to as filamentous. Throughout the last couple of decades, the filamentous form was commonly associated with pathogenicity, but recent genetic and animal studies have shown that both forms are needed for *C. albicans* virulence [15].
1.2 Oropharyngeal Candidiasis

Oropharyngeal candidiasis (OPC) is most prevalent in infants, the elderly, and compromised hosts and occurs in association with serious underlying conditions including diabetes, leukemia, neoplasia, steroid use, antimicrobial therapy, radiation therapy, and HIV infection [16,17]. One group of investigators reported that 28 % of cancer patients not receiving antifungal prophylaxis developed OPC and another group observed OPC in 57 % of immunocompromised patients [18]. Patients at greatest risk of developing OPC include those receiving corticosteroids and with prolonged neutropenia who are colonized with a Candida species [19]. Approximately 80-90 % of patients with HIV infection will develop OPC at some stage of their disease. Symptoms of oral thrush are variable, including a sore, painful mouth, burning tongue and dysphagia [20, 21]. 60 % of untreated patients develop an AIDS-related infection or Kaposi’s sarcoma within two years of the appearance of OPC [22]. Candida species colonise the oral cavity in 30-60 % of the general population. The ability of Candida albicans to adhere to buccal epithelial cells is critical in establishing oral colonization; Candida albicans adheres better to epithelial cells than non albicans Candida species. Low numbers of organisms are the result of effective antifungal host defense mechanisms in the oral cavity. Low salivary flow rates correlate with higher prevalence rate of Candida. Genotyping of Candida strains obtained from HIV positive patients with OPC and esophageal candidiasis compared to those isolated from healthy individuals indicate an identical distribution frequency, suggesting that HIV associated candidiasis is not caused by unique or particularly virulent strains, but from defects in host defenses [23].
Many predisposing factors have been identified as important in the development of oral candidiasis, including malnourishment, common endocrine disorders, such as diabetes mellitus, antibacterial drug therapy, corticosteroids, radiotherapy and other immunocompromised conditions, such as acquired immunodeficiency syndrome (AIDS) [24]. Oropharyngeal candidiasis is more common in smokers and patients with CD4 cell counts <200 cells/μL. Hazards of HIV disease progression in oropharyngeal candidiasis patients is 7.3 times more compared with non-oropharyngeal candidiasis patients [25].

Oropharyngeal candidiasis has four major presentations in patients with HIV infection. Pseudo-membranous candidiasis appears as white or yellow plaques, which may be located in any part of the oral cavity. This form is typically referred to as thrush. These lesions can be easily removed with a spatula. The underlying mucosa appears erythematous and may bleed. These lesions may be painful, and limit eating and drinking. Erythematous candidiasis presents as red areas on the palate, the dorsum of the tongue, and occasionally on the buccal mucosa. It is usually asymptomatic. Hyperplastic candidiasis is characterised by white plaques that do not rub off and can be confused with oral hairy leukoplakia. Angular cheilitis presents as fissuring at the corners of the mouth. Vitamin B₁₂ deficiency, diabetes and indinavir-associated desquamative cheilitis should be considered as differential diagnosis for angular cheilitis [26].
1.3 Vaginal candidiasis

Vaginal candidiasis is a vaginal mucosis opportunistic infection caused by species of the genus Candida in women, in the fertile period, and also the most frequent and important fungal disease of vaginal content [27]. Women around the world get diagnosed of vaginal candidiasis. It is estimated that 75% of women during the fertile period have at least one episode of vaginal candidiasis. Approximately 40-50% of women have repeated infection. Less than 5% of adult female population receives repeated, frequent attacks of recurrent vulvovaginal candidiasis. Point-prevalence studies indicate that Candida species may be isolated from the genital tract of approximately 20% (range 10-50%) of asymptomatic, healthy women in the child-bearing age [28]. 25-40% of women who are culture positive for Candida species in the vaginal area are asymptomatic carriers. The natural history of asymptomatic colonization is unknown, although limited human studies suggest that vaginal carriage may continue for several months and perhaps years. In the United States, Candida species is now the second most common cause of vaginal infections, while in Europe it is listed as the primary cause [29]. Vaginal candidiasis is associated with many mental and emotional problems [30]. Documented risk factors of vaginal candidiasis are pregnancy (30-40%), use of high estrogen content oral contraceptives, antibiotics, steroids, chemotherapeutics, attendance at sexually transmitted diseases clinics and age [31]. The increased secretion of reproductive hormones during pregnancy favors the formation of infection [32]. High levels of estrogen provide an increased amount of glycogen in the vagina, furthermore providing a good source of carbon required for candida growth and their germination. These hormones accelerate the formation of yeast pseudopyphae. Vaginal candidiasis is rare in
postmenopausal girls and women, due to hormonal dependence of vaginal candidiasis. There is a balance between candida, normal bacterial flora, and immune defence mechanisms. When this balance is disturbed, colonization is replaced by infection. It is not concretely evident as to what exactly leads to disruption of the balance and origin of infection. Vaginal candidiasis occurs when there is increase in the virulence of candida, and as a result of the reduction in local defence mechanisms. The exact mechanism by which candida infection occurs is not clear. It is possible that there are multiple mechanisms by which candida can cause cell damage and lead to direct invasion of the infection hyphae in epithelial tissues [33]. During vaginal candidiasis, vagina is the normal pH range (pH 4.0-4.5), as opposed to mixed infections (bacterial, trichomonas), where pH rises to levels greater than 4.7. Percentage of infection that causes C. albicans was high in the past decades, and varied from 85 to 90 % [34]. The clinical symptoms of vaginal candidiasis are nonspecific, and a broad variety of infectious and noninfectious diseases can cause similar symptoms. Women with vaginal candidiasis do not notice any change in their vaginal secretions. Vulvovaginal itching, irritation, soreness, burning, or dyspareunia are more common symptoms of vaginal candidiasis [35]. Occasionally, vaginal candidiasis causes external dysuria. On vulvar examination, patients may exhibit redness, swelling, fissures, or excoriations, and vaginal signs of erythema or a thick curdy discharge may be seen [36].
2. Cancer

Cancer is an abnormal growth of cells that grows and spreads through uncontrolled cell division. These ‘malignant’ cells may invade other tissues and spread (metastasize) to more distant parts of the body. Cancer is not one disease but a group of more than 100 distinct disorders. It is the world’s second biggest killer after cardiovascular disease and was responsible for the death of 7.6 million people in 2005 [37]. Globally the number of people diagnosed with cancer is estimated at around 11 million people, a figure that is set to rise to 16 million by 2020 [38]. Of all new cancer cases, it is estimated that one third could be cured if they were adequately diagnosed and treated [39].

2.1 Oral cancer

Oral cancer refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, floor of the mouth, oropharynx, buccal surfaces and other intra-oral locations, according to the International Classification of Diseases. Nevertheless, the term is synonymous to squamous cell carcinoma (SCC) of oral mucosal origin that accounts for more than 90% of all malignant presentations at the aforementioned anatomical sites [40].

Oral cancer though uncommon in developed countries is a serious and growing problem in many parts of the globe. Oral and pharyngeal cancer, grouped together is the sixth leading cancer in the world and ranks in the top three in high incidence areas. The annual estimated incidence [41] is around 275,000 for oral and 130,300 for pharyngeal cancers excluding naso pharynx; two thirds of these cases occurring in developing countries.
In high-risk countries such as Sri Lanka, India, Pakistan and Bangladesh, oral cancer is the most common cancer in men and may contribute up to 25% of all new cases of cancer. In low incidence countries, such as United Kingdom, oral cancer accounts for ~3% of all malignancies. In the context of the European Union (EU) countries in 2004, there were 67,000 new cases. Overall in the EU, oral and pharyngeal cancer occupies the seventh position [42]. The lifetime risk of developing oral and pharyngeal cancer in Europeans is estimated at 1.85% for men and 0.37% for women. The incidence rates are higher in Eastern Europe compared with Western, Northern or Southern Europe. Within the EU countries the highest male incidence rates are found in France and Hungary. In most countries around the world, oral cancer is more common in men than women. The reported sex differences are attributable to heavier indulgence in risk habits (tobacco and alcohol) by men and exposure to sunlight (for lip cancer) as a part of outdoor occupations. The ratio of males to females diagnosed with oral cancer however, has declined over decades and is now about 1.5:1 for the mouth and about 2.8:1 for cancer of oropharynx. Thus oral/pharyngeal ratio is lower in men than women suggesting some male characteristic may predispose preferentially to pharyngeal cancer. The risk of developing oral cancer increases with age and the majority of cases occur in people aged 50 or over. About 6% of oral cancers occur in young people under the age of 45 years [43]. In high incidence countries of the world, many cases are reported before the age of 40. The rising incidence in oral and oropharyngeal cancer and mortality rates in young adults were first reported in Scotland [44] and Denmark [45] and now appear to be a common finding in many countries in the European Union and parts of United States [46,47].
Asians have a higher risk of oral cancer compared to other population groups and the racial/ethnic disparity in oral cancer rates in the world is largely attributable to life-styles, particularly chewing tobacco and areca nut consumed in betel quid by Asian groups [48]. For most countries, the overall five year survival rates for cancers of the tongue, oral cavity and oropharynx are around 50–60 % [49]. The best outcome is for cancer of the lip with over 90% of patients surviving five years. The most important risk factors are tobacco, excess consumption of alcohol [50] and betel quid usage [51]; these factors acting separately and synergistically together. Attributable risk of oral cancer due to tobacco and alcohol combined is estimated to be more than 80 %. Heavy drinkers and smokers have 38 times the risk of abstainers from both products [52]. All forms of tobacco are carcinogenic and evidence for smokeless tobacco causing oral and pharyngeal cancer have recently been evaluated and confirmed [53,54]. Other factors such as HPV infection may also be involved [55] particularly for tonsil and oropharynx in young people [56]. Among young people (under the age of 45 years) there is a sub-group of patients (about 25 %) who probably have not had any exposure to these major risk factors [57, 58].

2.2 Cervical cancer
Cervical cancer, a malignancy of the cells that line the surface of the cervix. Cervical cancer usually begins as asymptomatic pre-cancerous lesions known as Cervical Intraepithelial Neoplasia (CIN) and or cervical dyaplasia, which develops gradually over many years. Cervical cancer has a very good prognosis (overall 74.0 % 5-year survival) and with early detection and treatment, the mortality is even lower with 5-year survival more than 90 %. There are two main types of cervical cancer: squamous cell carcinoma
(SCC) and adenocarcinoma (ACC). SCC is the more common type of cancer, accounting for about three quarters of all cases [59]. Long term studies suggest that invasive disease arises as a consequence of progression from mild dysplasia through severe dysplasia to carcinoma in situ [60,61]. These precursor lesions are also known as cervical intraepithelial neoplasia (CIN).

Cervical cancer is, after breast and colorectal cancer, the third most common cancer among women worldwide, responsible for 529,000 new cases and 275,000 deaths in 2008 [62]. The implementation of population-based screening programs for cervical neoplasia in developed countries since the 1960s has caused a strong reduction in cervical cancer incidence [63], while in developing countries cervical cancer still accounts for 13% of the female malignancies. Infection with high-risk human papillomavirus (hr-HPV) has been identified as the most important factor in development of cervical cancer [64]. Therefore, improving cervical cancer screening by HPV DNA testing and vaccination against HPV are nowadays of major interest [65, 66]. Risk factors for cervical cancer include socio-demographic factors, including sexual activity (lifetime number of sex partners, early age at first intercourse, frequency of sexual encounters) age and parity, as well as factors related to health behaviour such as smoking, use of oral contraceptives, nutrition and regular screening [67, 68]. Some of these factors are now recognized to be proxies for exposure to HPV [69]. HPV itself is no longer considered a risk factor, but a causal factor for cervical neoplasia, as HPV is present in virtually all cervical cancers. This implies that HPV is the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer [70]. The most important determinant of risk of HPV infection is age, and most studies show a sharp decrease in prevalence after age 30. This
increase seems to be independent of sexual activity [71, 72]. HPV however, is not a sufficient cause, and cofactors have a role in the persistence of HPV infection and occasionally in the progress to cervical neoplasia and ultimately invasive cancer [73]. Determinants of persistent HPV infection of ≥ 6 months include older age, infection with multiple types of HPV, infection with a high-risk type at the previous visit and a high viral burden in subsequent samples [74, 75].

2.3 Colorectal cancer
Cancer of the colon (colonic cancer) and of the rectum (rectal cancer) is collectively referred to as a single disease called colorectal cancer. The tumor is located in the colon in about two thirds of patients and in the rectum in the remaining third of patients. Worldwide, annually more than 1 million patients develop colorectal cancer (CRC) and over 600,000 patients die from it each year. Colorectal cancer is the third most common cause of cancer related death after lung and gastric cancer. The incidence of colorectal cancer is relatively high in the western world and steadily increasing [76, 77]. In the general population, the life time risk of developing sporadic colorectal cancer is 5-6 % [78]. The most frequent initial symptoms reported by colonic cancer patients are vague symptoms like tiredness because of anaemia, weight loss, nausea, decreased appetite, while some also report change in bowel habits and abdominal pain. Rectal cancer patients report rectal bleeding and change in bowel habits as their most frequent symptoms [79]. None of the symptoms are predictive of colorectal cancer and they all are ill-defined except rectal bleeding.

There are many potential CRC risk factors including consumption of red/processed meat and alcohol, body and abdominal fatness, adult attained height, smoking, infectious
agents, radiation, industrial chemicals, some medications and unsaturated fat. There are several mechanisms by which consumption of red and processed meat may lead to CRC. High temperatures used during cooking of meat can result in the formation of heterocyclic amines, which are potent carcinogens [80]. Processed meat, often defined as meat preserved by smoking, curing, salting or adding preservatives, often contains large amounts of salt, nitrite and nitrates. Degradation products of amino acids can react with nitrite and nitrate, forming $N$-nitroso compounds. Haem iron in the diet can also increase the amount of carcinogenic $N$-nitroso compounds and can lead to the production of free radicals [81]. High body and abdominal fatness increase the risk of CRC. Abdominal fatness, measured by the waist circumference and/or waist to hip ratio, in particular increases insulin resistance [82], which can lead to increased insulin production and an increased risk of colon cancer [83]. Obesity in general stimulates the inflammatory response which can lead to cancer, as the adipose tissue of obese individuals recruits macrophages, which secrete pro-inflammatory signal molecules and cytokines [84]. Height may also affect cancer risk as it is possible that the larger the number of cells in a body, the higher the chance of malignant transformation [85]. There is also convincing evidence that consumption of alcohol increases risk of CRC in males, and it probably also increases risk in females [86]. This may be due to higher alcohol consumption in men compared to women, differences in choices of drink, hormone-related differences in alcohol metabolism or susceptibility to alcohol. Ethanol is carcinogenic as it can inhibit DNA methylation, interact with retinoid metabolites and produce toxic metabolites such as acetaldehyde [87].