Oral squamous cell carcinoma: review of incidence and risk factors

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Abstract
Globally, oral cancer is the sixth most common cancer and it is associated with a mortality rate up to 50%. Oral cancer usually encompasses tumours derived from the lips, anterior two-thirds of the tongue, buccal mucosa, hard palate, the floor of mouth, upper and lower alveolar ridges, retromolar trigone, and sublingual area. An approximate age-standardized to world population (ASR (W)) for oral cavity and lip cancer according to the World Health Organization (WHO) the topmost is South East Asia with incidence of 6.4 per 100000, followed by Europe and East Mediterranean (4.6 cases per 100000), America (4.1 per 100000), Africa (2.7 per 100000), and Western Pacific area (2.0 per 100000). Oral squamous cell carcinoma has multifactorial pathogenesis which includes smoking, alcohol consumption, and HPV and others. Oral cancer has multifactorial etiology, mainly smoking, tobacco, alcohol consumption, betel quid chewing and high-risk human papillomavirus (HPV). Worldwide, the prevalence of HPV infection is 3% in oral cavity cancer and has a significant role in the management of oral squamous cell carcinoma (OSCC) as HPV-related oral cancers have shown better prognosis.
The risks of oral cancer in many developing countries had increased mainly by the habits of using betel quid chewing, tobacco and alcohol consumption. Human papillomavirus is a major concern and a public burden in a clinical setting all over the world. The sites frequently involved in HPV related cancers are tonsils and base of the tongue.

Keywords: Oral squamous cell carcinoma, incidence, risk factors

Oral Squamous Cell Carcinoma (OSCC)
According to National Cancer Institute (USA), oral cancers are defined as malignancy arising from epithelial lining of tissues of the oral cavity or the oropharynx (NCI 2018). Most of these cancers are squamous cell carcinomas (84 to 97%) (1, 2) which are mostly derivative of pre-existing “potentially malignant” lesion or more commonly, from the normal epithelium.
The term “oral cancers” is often used interchangeably with oral squamous cell carcinoma (OSCC) (Markopoulos, 2012). Global epidemiology of oral cavity cancers and oropharynx include cancers of the mouth (oral cavity), lip, tongue and oropharynx, excluding phyrangeal sites and the salivary glands (Warnakulasuriya, 2009).

Sites of OSCC
According to reports about 90% of the oral cavity carcinomas are OSCC (3, 4). Oral cancer usually encompasses tumours derived from the lips, anterior two-thirds of the tongue, buccal mucosa, hard palate, the floor of mouth, upper and lower alveolar ridges, retromolar trigone, and sublingual area (5, 6). Most frequently occurring is the Squamous cell carcinoma approximately 95% histological type (7).

Histology of OSCC
Cancer most frequently arises from a series of anomalies and changes of the epigenetic origin in the signalling pathways that resulted in multiple phenotypes which facilitate the development of OSCC (8). Squamous cell carcinoma is an invasive neoplasm of epithelial origin with a variable amount of squamous differentiation with or without a degree of keratinization. It is originated from keratinized stratified squamous epithelium i.e. skin or non-keratinized i.e. oral mucosa, uterine excocervical mucosa and oesophageal mucosa (9).

There are several histological types of OSCC which include conventional, verrucous, spindle, basaloid, adenosquamous, papillary, and acantholytic type (10). Oral squamous cell carcinoma has multifactorial pathogenesis which includes smoking, alcohol consumption, and HPV and others (11).

Oral squamous cell carcinoma can arise from several sites in the oral cavity but the most common sites are the lateral border of tongue and floor of the mouth, with a percentage of 20–40% and 15–20%, respectively (12, 13). Histologically, the lesion ranges from various stages i.e. preneoplastic changes to the formation of cancer. However, it should not be considered that all precancerous or reactional lesions will eventually change into amalignant tumour (8).

Potentially Malignant Changes in Oral Mucosa
The development of OSCC is frequently preceded by a series of distinct histopathological changes. The term oral epithelial dysplasia (OED) is the diagnostic marker of premalignancy which are confined to the surface epithelial layer (14).

Histopathological grading of OED can be used as a clinical tool to estimate the risk of malignant transformation and usually guides clinical management and treatment of patients (15). These changes often manifest clinically as an oral mucosal lesion. During carcinogenesis, histological characteristics of epithelium can be classified as either reactive epithelial changes or neoplastic epithelial changes. Reactive epithelial changes include hyperplasia, hyperkeratosis, and acanthosis. Neoplastic epithelial changes include mild, moderate, and severe dysplasia (16). Oral cancer initially emerges as an epithelial dysplasia and was described as altered proliferation on the surface epithelium followed by degeneration of the subepithelial basement membrane, lending to local invasion and metastasis. Local invasion is often characterized by the appearance of islets and cords of epithelial cells within the underlying connective tissue (17).
Incidence of OSCC

Generally, oral cancer is one of the most common cancer types and is considered a growing problem in public health around the world (18). Oral squamous cell carcinoma is the sixth most common cancer type in the world and third most common in South-central Asia (18, 19). Among cancers, lip and oral cavity cancer is 12th most common cancer with an incidence rate of 3.8%, 1.8%, and 2.1% in South, East, and West Asia, respectively (GLOBOCAN, 2012). These cancers are the result of aggressive tumours which originates from the oral cavity and the largest portion of oral cancer (lip, oral cavity, and pharyngeal cancer) was found in South Asia (48.7%) with a more male to female ratio (2:1) (Shield et al., 2017). According to a recent study, it has been reported that 14.1 million new cancer cases and 8.2 million cancer deaths happened around the world in 2012. Among those, 300,400 new cases and 145,400 deaths were reported due to the lip and oral cavity cancer, which accounts for more than 2% of new cases and 1.7% cases of death in the world, respectively (20). An approximate age-standardized to world population (ASR (W) for oral cavity and lip cancer according to the World Health Organization (WHO) the topmost is South East Asia with incidence of 6.4 per 100000, followed by Europe and East Mediterranean (4.6 cases per 100000), America (4.1 per 100000), Africa (2.7 per 100000), and Western Pacific area (2.0 per 100000) (Ferlay et al., 2013). The prevalence of OSCC is high in Asia (Southern parts), East Europe, Caribbean and Latin America. (18).

Risk factors for OSCC

Due to the indicative difference in exposure to environmental and behavioural risk factors there is a substantial difference in the global incidence of OSCC. Tobacco use (both chewing and smoking), alcohol consumption, betel-quid chewing and continued viral infection like HPV are considered as major risk factors for oral cancer (21). Despite the distinct role of tobacco and alcohol in oral cancer that is already established, the possible role of diet and oral hygiene are increasingly hypothesizing as independent risk factors (22).

Major Risk factors for OSCC

Tobacco consumption is still a major risk factor for OSCC. According to International Agency for Research on Cancer (IARC), tobacco smoking is classified as group one carcinogen (rated according to the severity of carcinogenic activity) for oral cavity cancer. Smoking habit is rising in low and middle-income countries (WHO, 2015). There is a dose-dependent relation between tobacco smoker and oral cancer, heavy smokers are at considerably higher risk of oral cancer as compared to low smokers and non-smokers in the absence of any co-existing risk factor. In fact, head and neck squamous cell carcinoma (HNSCC) risk considerably raised when frequency per day increase to 20 cigarettes and smoking duration is more than 20 years (23, 24).

After confirmation of risk of carcinogenesisto tobacco smoking and other additional confounding factors, some studies in America, Europe, and Asia reported heavy alcohol consumption association with OSCC (WHO, 2015). A meta-analysis showed that chances of HNSCC increase with increasing dose of alcohol consumption. Those who use a high quantity of alcohol are at more risk to develop HNSCC as compared to those who use low quantity of alcohol (Turati et al., 2012).
Heavy tobacco users have 20 times more risk; heavy alcohol users have 5-fold higher risk and 50-times more risk for those who use both tobacco and alcohol. There is a synergistic effect between alcohol users and tobacco consumption (25).

Betel quid chewing is a frequent habit in various regions of Asia as well as Asian migrants worldwide (Petti et al., 2012). The habit produces addictive psychostimulation with complaisant effects and is deeply rooted in many cultures (Petti et al., 2012). The carcinogenic effect of betel quid is already established, and the carcinogenic effect is attributed to tobacco. The odds ratio (OR) in HNSCC for betel quid chewing with tobacco is 7 to 8, and 3 to 6 for betel quid without tobacco (Guha et al., 2014). In Southeast Asia Betel-quid chewing is also a major risk factor.

Minor Risk Factors for OSCC

Poor oral hygiene could also cause carcinogenesis. Some studies exhibit the correlation between oral cancer and bacterial load which is abundance in poor oral hygiene, chronic periodontitis, and poor dental status (Fitzpatrick and Katz, 2010; Gondivkar et al., 2013; Ahrens et al., 2014). Beside major risk factors, dietary habits can have a relevant aspect in oral cancer. One author suggested that fruit, vegetables, animal origin products and poor in meat diet had a better role against oral cancer (Braviet et al., 2013). Some researchers reported findings that high deficiency of vitamin D in oral cancer patients (Lipworth et al., 2009; Grimm et al., 2015). However further investigation needed for the role of vitamin D in oral cancer.

The immune system plays an important role in carcinogenesis. Human Immunodeficiency Virus (HIV) infection and organ transplants patients have a high incidence of developing oral cancer as compared to the general population (Van Leeuwen et al., 2009; Collett et al., 2010). Environmental pollution might be playing a carcinogenic role as well as researchers had shown heavy carcinogenic element in the soil of Taiwan (Chiang et al., 2010). However, supporting data is not consistent.

Pathophysiology of OSCC

The tumorigenic genomic changes are of two main types i.e. tumour suppressor genes (p16 and p53), which when inactivated, stimulate tumour development through genetic mutation, loss of heterozygosity, or deletion, or by epigenetic modifications such as remodeling of chromatin; and oncogenes (myc, erbB-2, Epidermal Growth Factor Receptor (EGFR), cyclin D1, which stimulate the growth of tumour upon activation through overexpression due to amplification, increased transcription, or changes in genetic structure (Huang et al., 2006; Diez-Perez et al., 2011). Both kinds play a significant role in the pathogenesis of OSCC. Alteration in p53 and p16 are related to carcinogenesis process as p53 is responsible for regulating cell proliferation, DNA repair and apoptosis, whereas p16 regulates the cell cycle. Mutation in p53 is predominately related to usage of tobacco and smoking in HNSCC (Hashibeet al., 2009).

Chemical Mediators

Endothelin-1 (ET-1), proteases and nerve growth factor (NGF) are involved in oral cancer. ET-1 is a vasoactive peptide that generates nociception by binding to endothelin-B receptors and signify on dorsal root ganglion satellite cells and non-myelinating Schwann cells (Pickering et al., 2008; Schmidt, 2015). Protease-activated receptor type 2 (PAR2) is also participating in oral cancer and this receptor is stimulated by serine proteases, tryptase.
and trypsin (Russo et al., 2009). Due to continuing action of serine proteases, sensory neurons of many microenvironment cancer exposed NGF (Jemal et al., 2011). Cell proliferation and invasion of oral cancer can be promoted by nerve growth factor NGF (Kolokythas et al., 2010).

Neovascularization

“The growth of new blood vessels (neovascularization) from pre-existing ones, is a multi-step process, which appears to be regulated by both stimulatory and inhibitory factors and is vital for the continued growth and survival of solid neoplasms” is defined as angiogenesis (Wadhwan et al., 2015). Angiogenesis is a key step in abnormal cell growth and metastasis of a tumour. Several different angiogenic factors have been involved i.e. vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), transforming growth factor beta (TGF-β), interleukin-8 (IL-8) (Grothey and Galanis, 2009; Deryugina and Quigley, 2015). Of these, expression of VEGF family, VEGF-A and VEGF-C are the important types which have been reported in OSCC and are majorly associated with metastasis (Friedrich et al., 2010; Okada et al., 2010; Kapoor and Deshmukh, 2012; Zhao et al., 2013).

Oral squamous cell carcinoma is a diversified process in which multiple genetic alterations occur that leads to downregulation of tumour suppressor genes. These multiphasic events can eventually result in mutation of angiogenic growth factors (Calixto et al., 2014).

Human Papillomavirus (HPV)

HPV Genomic Structure

Structurally, HPV is seen as a closed circular double-stranded deoxyribonucleic acid (DNA) genome and this virus is characterized by a non-enveloped icosahedral capsid with a virion size of approximately 55 nm in diameter (26, 27). The DNA of HPV is around 8 kb in size which are divided into three major regions i.e. early (occupies over 50% of the virus genome), late (40% of the virus genome), and a long control region (LCR; 10% of the HPV genome). The molecular arrangement showed that all HPV have a same genomic organization with 8-9 open reading frames (ORFs) on corresponding strands. The gene expression of HPV is not fully understood however, it is believed that genomic expression leads to the expression of six viral non-structural regulatory proteins (E1, E2, E4, E5, E6 and E7) from the first coding section late genes codes the major and minor capsid proteins L1 and L2, respectively, while the second coding section undergoes for terminal differentiation. The third section holds the LCR which is confined to ORF L1 and E6. All HPV genomes show a different length of LCR (Fertey et al., 2011).

HPV Life Cycle

The replication cycle of HPV is closely related to differentiation of the epithelium that it infects. The infection first enters the basal layer of the epithelium where they remain in less number of copies. After reaching inside the cell, uncoating of the circular virus genome occurs and is further transported to the nucleus. Deoxyribonucleic acid (DNA) replication will start after HPV leave the cells and this phase is called productive phase, where they make more than 1000 copies per cells. After that, expression of late genes begins and finally viral particle produced and released (Tommasino, 2014). Even though the oncoproteins, E6 and E7 are also expressed soon after infection, it is difficult to assess the exact temporal lineage of initial events in the virus life cycle. One of the reason is that it is still very complex
to infect the cells with HPV and follow the sequence of infection. However, the infection may continue inside the infected cell, its daughter cells, and in the basal layer of the epithelium over a long period of time which can last up to several years (McKinney et al., 2015).

**HPV subtypes and Diseases**

Human papillomavirus is one of the most frequent causative agents in disorders of the skin and mucosal epithelia. The diseases range from common benign warts of the hands to potentially invasive cervical cancer. Human papillomavirus has over 170 subtypes which are divided broadly into two groups as low-risk (e.g. types 6 and 11) and high-risk (e.g. types 16 and 18)(28). Low-risk HPV can cause genital warts, while high-risk HPV is associated with malignant lesions such as oropharyngeal, cervical neoplasm, penile, and vulvar carcinomas (29).

**HPV as a Predisposing Risk Factor in OSCC**

HPV infection as an aetiology has been identified recently as a major risk factor for OSCC along with the use of tobacco and alcohol consumption. Sexual behaviours including open-mouth kissing are among the most likely reasons for oral HPV infection (30-32). It has been studied by Gan et al. and found out that HPV is more frequently detected in smokers and tobacco users as compared to non-smokers and non-tobacco users (33). However, the detection is more common in patients with greater than a one-lifetime sexual partner and with the oral sex history. As per past evaluation by IARC on HPV, the current figure estimated that 25.6 % of all cancers of the oral cavity and oropharyngeal origin are associated with HPV infection, with HPV 16 in high persistence (Bruni et al., 2017). Moreover, almost all HPV-positive cancers are strongly associated with HPV 16 and 18 (34).

Within the HPV family, there is more prevalence and a significant association with OSCC among high-risk HPV types (HPV 16 and 18) compared to other low-risk types. The probability of detecting high-risk HPV in OSCC was estimated to be 2.8 times more than that of low-risk HPV (35). In a study by Zhang et al., it has been found that 74% of OSCC were positive for HPV 16 and 18 DNA compared to the normal oral mucosa, which is reported to be fifty-five per cent(36). In a case-control study conducted in the Mexican population, a strong evidence between HPV and OSCC has been observed. Moreover, it has been found that the prevalence of HPV was more in OSCC cases (43.5%) compared to the control (17.3%) with the most frequent types were HPV 16 and 18 among OSCC cases (37). A meta-analysis by Miller et al. on HPV has shown that the possibility of detecting HPV in the oral mucosa of OSCC patient is 46.5% compared to HPV in normal oral mucosa which is 10% (35). Few studies on Indian population have also shown the similar prevalence rate of HPV in OSCC patients as 70.59% in Karnataka, 45% in an unknown place in India, 43.54% in Northeast India (38-40).

Besides these, there are few published studies on Australian (6%), Indian (0% to 1.6%), Malaysian (3.3%) and German (6%) population which have also shown low to zero prevalence of HPV in OSCC (41-45).

Based on these studies, it is believed that there is a strong association between HPV and HPV-related OSCC. The high-risk HPV types possibly have a more significant
association with OSCC, compared to low-risk types. Moreover, the incidence of HPV-positive OSCC has increased significantly in recent decades.

There is a tragic increase in HPV associated HNSCC in the world with some variations according to gender, ethnicity, and geographical location. HPV is an etiological factor, has been established recently by the International Agency for Research on Cancer (IARC) for oropharyngeal squamous cell carcinoma (46). The prevalence of HPV related head and neck cancers (HNC), especially oropharyngeal cancer is more in North America (70%) and Europe (50%) when compared to rest of the world (47). A rising trend has been seen in Australia, where HPV-positive oral pharyngeal squamous cell carcinoma (OPSCC) gradually raised from twenty percent to sixty-threepercen of cases over the recent two decades (48). A recent study on Bangladeshi population has shown 21% high-risk HPV infection in HNSCC (49). Furthermore, a study in India has shown high-risk HPV detection (13.7%) in HNC (42). A meta-analysis from 2002 to 2012 performed on European population has shown that prevalence of high-risk HPV is forty percent in HNC (50). A meta-analysis by Ndiaye et al. included 148 studies from 44 different countries and has shown 31.5% HPV detection in HNSCC (51). There is an increased incidence of HPV-related HNC in Taiwan from 1995 to 2009 which has been found in most of the younger patients as compared to non-HPV associated HNC. The overall incidence of HNSCC is also rising in Taiwan and this is an alarming issue (52).

It has been suggested that increased incidence of HPV related to early sexual exposure, high numbers of sexual partners and oral sex habits (53). Nowadays, HPV status is very important prior to treatment planning because HPV-associated HNSCC patients have a far better prognosis despite the stage of the tumour, age, or gender (54, 55).

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