ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 06, pp.52169-52178, June, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

ATTAINMENT OF HIGH RISK FACTORS AND SITE DISTRIBUTION OF ORAL SQUAMOUS CELL CARCINOMA IN YOUNG POPULATIONS

[1,2]Dr. Dusabe Emmanuel, [1,3]Dr. Lin Jie, [4]Dr. Mazimpaka Patrick, [5]Dr. Huang Zhibin, [6]Simon Afewerki Gebremedhin and *,[1]Prof. Cao Yingguang

[1]Faculty of Clinical Stomatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST), Wuhan, China
[2]Dental Department, Masaka District Hospital, Kicukiro, Ministry of Health, Kigali 250, Rwanda
[3]Department of Stomatology, Shenzhen People's Hospital, Shenzhen, China
[4]Rwanda Military Hospital, Section of Orthodontics and Dental Facial Pedics, Kigali 250, Rwanda
[5]Department of Stomatology, Zhongshan Hospital, Xiamen University, Xiamen, China
[6]School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ARTICLE INFO

Article History:
Received 23rd March, 2017
Received in revised form
14th April, 2017
Accepted 28th May, 2017
Published online 20th June, 2017

Key words:

High Risk Factors, Oral Squamous Cell Carcinoma, Young Populations.

ABSTRACT

There are many reports talking about rising incidence of oral cancer from many parts of the world, this incidence has gone up reasonably. It is known that oral cancer increases with person's age, previous studies have demonstrated an increasing incidence of tongue cancer and in the mouth of young males. Several studies by many authors also suggested that 4 to 6% of oral cancers occur at ages younger than 40 years. The studies provided evidence about risk factors for oral cancer and patients who have never smoked or consumed alcohol which are known as risk factors in older population with too short duration for malignancy transformation to occur. There is a multifactorial risks for this disease in young population including occupational, familial risk, immune deficits as well viral infections. Conflicting evidence has also been reported on the sex distribution and outcome compared with older patients. Therefore further more researches are required to understand demography involvement of the disease, high risk factors about this disease, current innovative diagnostic modalities and its prognostic markers.

Citation: Dr. Dusabe Emmanuel, Dr. Lin Jie, Dr. Mazimpaka Patrick *et al.* 2017. "Attainment of high risk factors and site distribution of oral Squamous cell carcinoma in young populations", *International Journal of Current Research*, 9, (06), 52169-52178.

INTRODUCTION

Basing on international agency for research on Cancer Incidence and Mortality, approximately 550 000 new cases of head and neck cancer (HNC) are diagnosed worldwide annually [1]. Furthermore, an increasing incidence of head and neck neoplasms among young adults (YA) has been reported in some studies in particular, reports indicate an increase in tumours affecting the tongue and oropharynx among young adults in India, Europe, the USA as well China [2-5]. It is known that oral Squamous Cell Carcinoma (OSCC) is the most frequent malignant neoplasm of oral cavity corresponding to 80 to 90% of all malignancies [6]. The oral squamous cell carcinoma is a particular type of cancer classically described as a tobacco and alcohol-related disease affecting mostly elderly male patients. However, epide-miologic studies have demonstrated an increasing incidence of young individuals with oral cancer. Interestingly, the clinicopathological profile, etiology, risk factors, and outcome of patients with early-onset disease seem to present several differences compared to late-onset oral carcinoma. As reported by Patel and other retrospective studies including elderly and young patients, it has been shown that the incidence of squamous cell carcinoma (SCC) of the mouth in young people is low but presents an increasing tendency [7]. Many authors consider young patients as those who are under 40 or 45 years [8-11], whereas few investigations select individuals under 20 or 30 years [12-14]. In patients younger than 40 years, the incidence of oral cancer varies between 0.4 -3.6%, but it can reach 6.7% in studies considering 45 years as the cutoff point [2]. The constraint is that most of investigations deal with a small sample of the patients due to its rarety in this group of young population , thus conflicting results have been published regarding the epidemiological aspects of oral SCC. The clear male predominance found in late-onset lesions is not found in the

******Corresponding author:* **Prof. Cao Yingguang,**
Faculty of Clinical Stomatology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST), Wuhan, China.

early-onset counterparts. Halboub and Ribeiro demonstrated that men are still more affected than women but only slightly more, with a F:M ratio varying from 1:1.2 to 1:4.9 [15, 16]. These findings reveal an evident rise of young women affected by oral SCC. The differences between sex distribution previously observed may be due to smoking and drinking habits, which are more socially acceptable for both genders currently [2]. Some previous articles have reported a predominance of oral SCC in young male patients [16-22]. This is in contrast with a study done by, Kuriakose *et al*, comparing oral squamous cell carcinoma in younger and old Indian patients. In their study, the authors reported a slight predominance of female oral SCC patients in the younger age group [23]. These kind of variations may be due to different geographic locations and social lifestyles between studied populations.

It is difficult to distinguish most of clinical features of OSCC in younger patients and in older patients, however many clinicians tend not to include OSCC as a differential diagnosis in young patients because this disease does not often present in that age range. [24] In our current literature search, we found that the tongue remains the most common oral subsite for SCC in young patients , with 39-77% of the cases [5, 25]. However in a recent study conducted in Taiwan by Ho, the study found that there is a higher incidence of oral SCC in the buccal area (53.6%) when compared with the tongue (42, 8%), but also betel chewing habit was common among these patients [26]. Other retrospective reports in Germany and Brazil showed a slightly higher incidence of oral SCC in the floor of the mouth, followed by the mobile tongue [16, 17].

Other epidemiological studies have also shown slight differences and similarity in sites of occurrence of oral cancer, however tongue, lip, and floor of the mouth are the most frequent sites of lesions of squamous cell carcinoma in the oral cavity [27-31] . Sharma P, *et al* conducted a study in western Indian population, and they reported that buccal mucosa was the common site, followed by retro molar area, floor of mouth, lateral border of tongue, labial mucosa, and palate Due to the fact that most patients tend to keep the tobacco in the form of quid in the buccal sulcus with close proximity to alveolus [32] , other few studies found the lip to be most constant site of squamous cell carcinoma in the oral cavity, with higher UV ray exposure which is attributed to be high risk factor of it [33]. Basing on its clinical presentation, some authors found that the typical clinical appearance of oral SCC is an ulcer ,often intermixed with white plaque and or reddish areas, these lesions in young patients were predominantly invasive compared with the exophytic lesions found in older patients [2, 23], in contrary, Falaki *et al*. reported exophytic lesion with ulcer as the most common clinical presentation in younger individuals [34].

Here are some symptoms of oral SCC, initial local pain which is uncommon [35]. Other signs and symptoms can be dysphagia, weight loss and otalgia (26.5%, 26.6% and 37.5%, respectively) [36], all these symptoms may seem to be related to the size of the lesions but also to anatomical location of the tumor. The duration of the symptoms before diagnosis can vary, but some studies reported that most of the patients had early stage disease at the moment of diagnosis, that is from 52-95% of the patients presented with lesions graded as T1 or T2, usually without neck metastasis [25, 37]. In another study done by Fang *et al.* He reported that 80% of patients younger than 40 years-old with oral SCC presented lesions staged as T1 or T2 and only one tumor with positive node metastasis, appearing to be weakly aggressive at diagnosis, However, the clinical result was poor, as 10 (66.7%), patients exhibited recurrence and five (33%) patients succumbed to the disease [38]. As reported by some authors, the time of delay before diagnosis is usually between few weeks and 10 months [39, 40]. The etiology of OSCC differs between young and elderly patients as reported by many previous studies [7, 34, 41-43]. As well some authors have suggested that younger patients with OSCC are likely non smokers and non drinkers [34, 43, 44]. Therefore, other factors might be associated with OSCC in young population, such as genetic predisposition, immunological and nutritional alterations and infection by HPV [41, 44, 45] . However, several studies found that this relationship is still not well established , especially in terms of biological behavior as well as clinical prognosis. Evidences suggest that there is an high increase of OSCC in younger patients compared to those affecting elderly patients [12, 41, 46]. Defining prognostic characteristic may be difficult for both younger and elderly patients, therefore regional lymph node metastasis, tumor location and TNM classification of malignant tumors (TNM) has been cited as prognostic indicators [47]. This article aimed to review the high risk factors contributing to the development of oral squamous cell carcinoma in young populations as well the site distribution of the disease in order to provide enough information for treating clinicians, epidermiologists in the field of dentistry and medicine.

High risk factors of oral squamous cell carcinoma

Tobacco and alcohol

Many studies proved that alcohol and tobacco consumption are the main risk factors of oral cancer [48-50]. In recent years, an increasing number of young patients, who declare to never having smoked or consumed alcohol excessively, are diagnosed with oral SCC [17, 31]. Tobacco smoke and alcohol abuse are considered well-established risk factors for oral SCC in older population. Apart from that, in young patients, these classical risk factors cannot be considered as the major ones for oral cancer [10, 17, 32, 33], if the period of abuse is not enough to create carcinogenesis [10]. On the other side, some studies reported that tobacco use starts during adolescence [10], usually before 16 years old , making probable that before the age of 40 years, patients have an accumulated risk of more than 21 years of consumption, being more susceptible for the oral cancer [34]. Probably, the pathogenesis of oral SCC in young people involves multiple factors, as genetic and other new behavioral factors [32, 33]. It seems that tobacco and alcohol consumption are not the main etiological factors for oral SCC in young patients.

Khat (Qat) chewing

Khat (Catha edulis Forsk) is a plant cultivated in territories of Somalia, Ethiopia, Djibouti, South and North Yemen, Madascar, Tanzania and down to South Eastern Africa. The leaves of this plant are extensively consumed by these populations. Qat leaves are generally placed in the mouth in the lower distal mucobuccal fold and are chewed during social-cultural gatherings, creating a noticeable pouch, where the duration of chewing may usually last up to several hours at a time. In a recent cross-sectional study it was found that qat

chewing caused loss of periodontal attachment presenting either as increased pocket depth or gingival recession [51]. One of the most important considerations from an oral health point of view is the relationship between qat chewing and the development of oral cancer (OSCC) and pre-malignant lesions. Qat chewing has been associated with an increased rate of oral cancer. Soufi *et al*. speculated that there may be a link between qat chewing and oral malignancies. In some of the cases in the study, the malignant lesion developed at the site where the qat bolus was held. All subjects in this small retrospective study were non-smoking qat chewers [52, 53]. Another study done in Southern Arabia found that the practice of qat chewing was prevalent in patients with head and neck OSCC [53]. One study found that half of qat chewers develop oral leukoplakias [54]. This becomes a significant finding if we are led to believe that such lesions become cancerous in 2-12% of these patients as concluded in some studies [54, 55] . In contrast, Macigo *et al*. [56], undertook a relative risk assessment, looking at the association between oral leukoplakia and use of tobacco, alcohol and qat in Kenya and concluded there was no association between oral leukoplakia and qat, whereas qat chewing, as mentioned above, has been reported to induce oral keratotic white lesions, but unlike tobacco use and chewing of betel nut, no direct association between the white oral mucosal lesions in qat users and development of oral malignancy was identified. [56, 57]. Studies focusing on other socio-cultural practices showed that the prevalence of oral cancer and other precancerous lesions such as oral leukoplakia in the Yemen was related to shammah use (traditional smokeless tobacco), which is a widely practised habit in the population that also use qat [58]. Ali *et al*. [59] looked at histopathological changes in oral mucosa induced by qat chewing, forty oral mucosal biopsies were taken from the buccal mucosa on the side preferred for qat chewing; 20 biopsies were taken from the opposite side and ten biopsies from the buccal mucosa of a non qat chewing control group. Even though histopathological changes were seen in the oral mucosa on the chewing side, these changes showed no evidence of malignancy. Another study also reported histopathological changes in the oral mucosa associated with qat chewing. These included acanthosis, abnormal rete ridges and hyperkeratosis but no evidence of carcinoma [60].

Medicinal nicotine use

Tobacco smoke contains many chemicals other than nicotine that have been clearly shown to be the major etiologic agents in smoking-induced diseases [61]. In tobacco, as shown by Hecht, *et al* , nicotine can be nitrosated to form nitrosamines known as a group of potent carcinogens [62]. Nicotine itself has repeatedly failed to show carcinogenic effects, in one animal study, rats breathed in a chamber with nicotine at a concentration twice that found in the plasma concentration of heavy smokers. Nicotine was given for 20 hr a day, 5 days a week over a 2-year period. The authors found no increase in mortality or frequency of tumors in these rats compared with controls. Specifically, there were neither microscopic nor macroscopic lung tumors nor any increase in pulmonary neuroendocrine cells. Thus, even long-term exposure to inhaled nicotine at relatively high doses does not appear to have a carcinogenic effect, nevertheless other studies are needed to deeply explore this, [63] Many Researches have suggested a number of mechanisms by which nicotine might theoretically induce or promote carcinogenesis or tumor development under certain conditions. These include activation of Akt signaling pathways via nicotinic acetylcholine receptors in bronchial epithelial cells by nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone suppression of apoptosis), and promotion of angiogenesis [64-68]. Other clinical trial study of about 6,000 smokers found that nicotine gum can be used safely for up to 5 years without any cardiovascular illnesses or other serious side effects [69]. The 2008 U.S. Public Health Service panel on treating tobacco use and dependence also concluded that the risks of nicotine replacement therapy are theoretical at this point and likely to be small if present at all, particularly when compared with the alternative risk of continuing to smoke cigarettes. The panel confirmed that each of the nicotine replacement therapies approximately doubles a smoker's chance of success in quitting [70].

In brief, with Nicotine replacement therapy, there is some confusion in the mind of professionals and patients whether any prolonged and chronic use of nicotine replacement therapy (NRT) could have the potential to cause cancer as these agents contain pure nicotine. There is no clear evidence that medicinal nicotine causes cancer. According to a recent study based on surveillance data among patients with chronic obstructive pulmonary disease in US found no independent increased risk for any cancer among NRT users. However, the authors noted that the surveillance time of 5 years was short [69]

Alcohol Containing Mouthwashes

Nowadays, maintaining good oral health has become an integral part of our daily lives, For an effective cleaning of teeth via toothbrush, and to support tooth brushing, mouthwashes, and other inter-dental cleaners can be used for better oral hygiene. Thus, people might not feel so happy without using mouthwashes even after a thorough brushing [71]. Mouthwashes are kind of antiseptic solutions playing a significant role in decreasing the microbial load in the oral cavity. They can also be used as an aid in the treatment of gingivitis, periodontitis, oropharyngeal diseases and other inflammatory conditions [72]. Controversial relation between OSCC and regular use of alcohol-based mouthwashes has been risen recently by some authors. Ethanol is carcinogenic agent present as an ingredient in mouthwashes and it exerts its effects through secondary mechanisms by generating carcinogenic acetaldehyde leading to lipid peroxidation and enhancement of penetration of other carcinogens [71, 73]. Link between oral cancer and alcohol-containing mouthwashes was firstly published as a case/control study performed with 200 patients with oral cancer and 50 general surgical patients as a control group. The study identified 11 people who did not smoke or consume alcohol beverages, although 10 out of the 11 used mouthwashes, including nine who used a product with 27% of alcohol. The study also found no overall relative risk, thus the author reported no statistical significance of this the case/control study [74]. Other authors suggested to use alcohol-containing mouthwashes as long as they are used following proper guidance by dental professionals and instructions from manufacturers, other did not support this view, however they advised for clinicians to promote the use of non-alcoholic mouthwashes in order to minimize any potential increase in risk, and discourage longterm use of high alcohol-containing products. [75], In a large case-control study done by Winn with 342 case subjects and 521 control subjects from Puerto Rico with oral cancer, the authors affirmed that they were unable to evaluate the accuracy of the reporting of

tobacco, alcohol and mouthwash use and found no association between mouthwash use and oral cancer. Other case/control study of oral epithelial dysplasia among 127 subjects from large pathology laboratories, authors examined eight variables describing mouthwash use and the alcohol content of the products used, their findings were negative even for all those eight variables. They found that the relative risk varied inversely with the percentage of alcohol in the mouthwash used, even after the authors controlled for smoking and beverages. The conclusion made by authors was that there was no relationship between mouthwash use and oral epithelial dysplasia [76, 77]. In summary and also according to a review done by the Food and Drug Administration and the American Dental Association found that the evidence about oral cancer and alcohol-containing mouthwashes is inconsistent and contradictory [78].

Genetic factors

Genetic predisposition for cancer development at young age, especially in those patients with no recognized risk factors seems to be preponderant [34]. Chromosome fragility, DNA ploidy abnormalities and increased familial risk of head and neck SCC have already been reported in young patients [26, 34, 35]. Considering the familial risk, a clear significant relative risk of SCC exists in first-degree family members of those who suffered head and neck cancer [35], especially when there is no recognized risk factor associated. Oral cancer has been associated with higher chromosome fragility and instability in youngsters, compared to elderly [36]. Genetic instability is an important molecular mechanism for head and neck cancers. Gain and loss of specific chromosome regions in DNA are responsible for head and neck cancers, for example the 3p or 9p21 region, which are early events strictly related with head and neck cancer development, but that are not commonly seen in young people [35]. It is supposed that a completely different model of tumorigenesis exists, at a molecular level, in young people. One essential step for tumorigenesis is deregulation of normal cell cycle regulatory system, especially in genes that control G1 to 2 phase progression in cell cycle [37]. The amplification of the gene CCDN1 was noted to be more expressive in young people , CCDN1 is a protooncogene that encodes cyclin D1, a key regulator of G1 phase in cell cycle. [31].

The over expression of cyclin D1 was found to be more prominent in young people [31], and it was correlated with disease-free survival in younger and elderly patients. Instead of these findings, larger studies are required to confirm the prognostic value of CCDN1 in young patients [31], Some genetic component to cancer development in young patients is likely, particularly in those patients with no recognized risk factors. These patients have been shown to have increased DNA fragility, which may make them more likely to develop genetic abnormalities [79]. However, studies examining specific genetic alterations in Head and neck squamous cell carcinoma (HNSCC) as a function of patient age, including mutations in p53, p21, Rb and MDM2, [80, 81] and microsatellite instability, [82] have failed to find an increase in these abnormalities among young patients. Likewise, Koch and colleagues found tumors of nonsmokers with HNSCC to have fewer genetic abnormalities than those of their smoking counterparts, leading them to conclude that the genetic alterations in tumors from nonsmoking patients remain undiscovered. [83] Llewellyn and colleagues' larger series reported a positive family history of cancer in 75% of female and 59% of male subjects younger than age 45 with HNSCC, suggesting genetics, immunology, or some common environmental exposure may play a role in the development of HNSCC in the young [21]. A rare inherited cancer syndrome associated with HNSCC is Fanconi anemia (FA), an autosomal recessive syndrome caused by defects in DNA repair. FA carries a high risk of development of malignancy at a young age, with a median age of presentation of 31, and a cumulative incidence of HNSCC of 14% by age 40,[84]. Patients with FA and HNSCC are more likely to be female (2:1), with very few reporting tobacco use. Oral cavity is the most common site and the outcome is poor, with a 63% rate of second primaries and a 2-year overall survival of 49%.

Syndromes associated with head and neck squamous cell carcinoma (HNSCC)

However rare inherited syndromes have been associated with head and neck squamous cell carcinoma (HNSCC), for instance in laryngeal cancer in Bloom and Li Fraumeni syndromes,oral cancer in Bloom syndrome, xeroderma pigmentosa as well ataxia telangiectasia. Baez described the role of Familial HNSCC with germline mutations of p16INK4a [85]. with emerged development in genetics of dyskeratosis congenita, involvement of different mutations in components of the telomerase complex, whereby the primary defect appears to be dysfunction in telomere maintenance [86]. Fanconi anaemia, aplastic anaemia and myelodysplastic syndrome, all possess similar mutations and are all apart of same disease group On the point of malignant transformation, the telomeres are repeatedly shortened until they can reach a critical length that can precipitate a genetic crisis characterized by genomic instability of surviving cells with progression to neoplasm.

Behavioral and other factors

Marijuana consumption

Several cases reported in the existing literature [40, 87] suggest an association between marijuana smoking and head and neck cancers and also respiratory cancers, but this correlation is not conclusive. The use of marijuana has been speculated as a risk factor for oral cancer in young people [2]. The explanation is that marijuana smoke contains carcinogens similar to those in tobacco, and its smoking involves greater inhalation and longer retention of marijuana smoke [41]. However, the clarity about the potential of carcinogenicity of tetrahydrocannabiol (THC), which is the major psychoactive ingredient in marijuana, is not yet understood, but it is evident that cannabinoids have an effect in tumorigenic or antitumorigenic role [41, 88]. Marijuana use and its association with younger patients has led to suggestions that this may be an unreported risk factor in studies that have found fewer risk factors in younger patients. In the only studies to specifically address marijuana use in young patients, 2 of Llewellyn *et al*'s series both reported similar use of marijuana among young patients with oral SCC and young controls [21, 89]. Zhang and colleagues at Memorial Sloan Kettering Cancer Center looked at the incidence of marijuana use among patients with pathologically confirmed squamous cell carcinoma (all head and neck sites) compared with age-matched and sex-matched controls culled from their blood bank records [90], they found that most marijuana smokers from both groups were under the age of 55.

The authors showed an increased odds ratio for risk of squamous cell carcinoma among marijuana smokers, but, as the authors pointed out, whether their data was biased by the controls being blood donors and possibly less likely to be users of illegal drugs was unclear. In an age and sex-matched, case control analysis of HPV-positive and HPV-negative HNSCC at Johns Hopkins, Gillison *et al* found an association of HPV positivity and marijuana use that increased in strength with increasing cumulative marijuana use [90]. In contrast, the HPV-negative group was more strongly associated with traditional HNSCC risk factors (tobacco, alcohol, and poor oral hygiene).

No specific analysis of marijuana use and age with respect to HNSCC in this aforementioned study was found, but the study provided further evidence for a subgroup of patients who lacked traditional risk factors yet share the risk factors of HPV positivity and marijuana use that many have linked to younger patients. Also, the observed cohorts of younger patients with head and neck cancer that have been reported in previous decades are possibly a result of a wave of generations in which marijuana use had become more common place during the teenage years

Immunodeficiencies

Some chronic immunodeficiency states such as Bloom syndrome, Wiskott-Aldrich syndrome, or even immunosuppression regimes following organ transplantation and anemia of Patterson/Kelly/ Plummer Vinson syndrome, Fanconi anemia) [42], might play important roles in carcinogenesis in young people [41]. Specifically, Fanconi anemia has an associated higher risk for developing head and neck cancer, which is estimated to be 40% by the fourth to sixth decade of life. Mutations in telomerase complex are responsible for Fanconi anemia and regarding its malignant transformation, telomeres are repeatedly shortened precipitating a genetic instability, allowing the progression to a malignant neoplasia [42]. As revealed by some authors, another distinct group that compound young head and neck cancer patients is those with cancer during childhood. The probability of a second synchronous tumor or metachronous primary tumor is estimated in 3–12% in 20 years of survival. Also, chemotherapeutic drugs and radiation can induce malignancies as side effects [12, 91].

Diet

It is known that a diet rich in fruits and vegetables, with antioxidant properties, has a significant protective role against oral cancer [92]. In a study with a sample of 116 patients aged 45 years and younger, diagnosed with squamous cell carcinoma of the oral cavity between 1990 and 1997 from the south east of England , the author found a significant reduction in the risk of oral SCC among females who consumed three or more portions of fresh fruits and vegetables [43, 44]. However, this factor is preponderant for the population in general and there are no studies on specific dietary behavior for young people.[92, 93]. According to studies of Llewellyn and colleagues' series, a significant reduction in risk was found in subjects who reported consumption of 3 or more portions of fresh fruit or vegetables per day [21, 89]. Generally, a diet high in fruits and vegetables is inversely correlated with a risk of oral cancer, [94] and, based on Lewellyn's studies, this can also be applied to young patients which could play an important role in decrease of the risks for oral cancers. Antioxidants which include components such as vitamins, carotenoids, folates and fibers, are believed to act through counterbalancing the harmful effects of other carcinogens such as tobacco and alcohol. There is a big role played by Mediterranean diet which contains high proportions of fruits, cereals, olive oil, and vegetables along with moderate quantities of dairy products and low amounts of meat which has shown to decrease the risk of cancer . However, more studies are required to evaluate the effectiveness of such diets as a possible protector from OSCC [95, 96]

Viral infections

Human Papilloma Virus

The human papillomavirus (HPV) comprises a huge group of more than 50 subtypes of viruses able to infect the anogenital region and can be divided into two major subgroups: low-risk and high-risk types for cancer. The low-risk HPVs are usually responsible for genital warts, whereas the high-risk ones have oncogenic capability, leading to the development of cancer. The HPV-16 and HPV-18 are the major high-risk types that are present in anogenital and head and neck cancers [97]. Recent changes in the epidemiological profile of oral carcinoma have encouraged the research for new risk factors related to the development of oral cancer. For example, there has been a decrease in the tobacco-associated oral cancer and an increase of non-smoking white female young patients aged from 18–44 years who presented with oral SCC [98]. These facts, are associated with the established oncogenic power of HPV-16 in cervix carcinoma raised the hypothesis that HPV could be an etiological factor for oral SCC. Moreover, oral mucosa is highly exposed to chemical carcinogens, infections, and trauma, making it more vulnerable to carcinogenesis. Then, it has been postulated that abrasions caused due to this continuous exposure might make this mucosal surface more susceptible to HPV by making it easier for the virus to gain entry into the basal cells of oral mucosa [97]

Mechanism of human papilloma virus (HPV) in Carcinogenesis

The mechanism by which the high-risk HPVs promote the carcinogenesis has been already revealed. Once the cell is infected with HPV, the viral oncoproteins E6 and E7 are integrated to the cell genome and their expressions alter the host genome functions [97, 98]. HPV E6 and E7 proteins disrupt p53 and pRb tumor suppressor genes as well as numerous cellular proteins involved in carcinogenesis (BAK, telomerase, INK4A, E2F, cyclins A and E, WAF1, and KIP1)[98]. These accumulated defects in the genomic expression of the infected cells lead to cell immortalization and genomic instability by deactivation of control and regulatory mechanisms of cell apoptosis, cell cycle, and DNA repair [97, 98]. These mechanisms are essential for the development of cervix carcinoma, once HPV prevalence in this type of cancer is 100% [99]. The same is true for oropharyngeal SCC, with a HPV prevalence up to 90% [100, 101]. In oral SCC, the role of HPV still remains unclear. The anatomical structures of oropharynx, especially the base of the tongue and tonsils, seem to be more susceptible to HPV infection when compared to oral sites [41]. The prevalence of HPV in oral cancer may vary from 0 to 100% [102], and this may not be only due to ethno-geographical differences but to the sensitivity of the applied

diagnostic technique and to the site of the lesion [102]. The first issue to study the HPV prevalence in these lesions is the techniques employed to detect it. The most accurate ones seem to be the polymerase chain reaction for the HPV DNA and *in situ* hybridization. However, immunohistochemistry techniques can also be used but it can lose its accuracy in old specimens [44].

Many review studies have been done to find out the role of HPV in oral SCC, only nine split the groups between young and older people [35, 103-105]. Other studies have shown the negative impact for the patient's survival with presence of human papilloma virus [35, 105-107], was neutral in three other studies [53, 54, 59], and had a positive impact in only one investigation [57]. Despite of the proved role of HPV in the carcinogenesis of the cervix and oropharynx, it is still difficult to draw any conclusion regarding the role of the high-risk HPV types 16 and 18 in the oral cancer development. Perhaps the most widely studied virus in the head and neck cancer literature in recent years is HPV, a virus initially linked to cervical carcinogenesis that has now gained interest for its connection to cancer of the oropharynx, particularly the lingual and palatine tonsils [94, 108]. The increasing incidence of tongue and tonsil cancer among young patients has led some authors to suggest that HPV may be responsible for this trend [5, 109] although the connection between oral versus oropharyngeal cancer and HPV is controversial. [110, 111]. In a direct comparison between oral cavity, oropharynx, and larynx squamous cell carcinoma (SCC) samples from young less than(< 50 years) and old above (>50 years) patients, Sisk and colleagues found no significant difference by age in the rates of HPV positivity (50% vs 44%, respectively. [112]. The authors acknowledged that there was a small study that does not allow definitive conclusions on this matter. Similarly, Koch and colleagues did not find an association of HPV positivity with age in 305 patients with HNSCC [83]. In a case control analysis, conducted by Gillison and colleagues looking at HPV-16 status of 240 patients with HNSCC at Johns Hopkins, found a higher proportion of young patients (< 50 years) in the HPV-16–positive group than the HPV-16–negative group (33% vs 17%, respectively) [113]. Additionally, they found a strong association between HPV-16 positivity and oropharyngeal and lingual or palatine tonsil primary sites. In a multi-institutional, prospective phase II trial of chemoradiation for advanced HNSCC that included analysis of HPV status in the primary biopsy, the mean age of the 38 patients with HPV positive tumors was lower than the 58 with HPV-negative tumors (56 versus 60, respectively), but the difference was not significant [114]. However, this study did find a significantly better response and survival in the HPV-positive group, even when adjusted for age, tumor stage, and performance status.

Fakhry likewise found HPV positivity to be linked to a better overall prognosis [114], and this has been seen in several other studies as well, [94]. Although none of these studies specifically addressed young patients. Interestingly, improved survival was also seen with increasing copy number of HPV-16 in 35 patients with tonsil carcinoma in one study, suggesting that the connection between HPV status and response to treatment may be quite strong [115]. The Gillison and colleagues' case control analysis did not address prognosis, but they did find the HPV-16–positive group to be significantly less likely to have the typical risk factors for HNSCC (tobacco, alcohol, poor dental hygiene) [94]. Funk's Group III patients fit into this description. Clearly, more research is needed into the role of HPV in HNSCC and its connection to treatment response, as well as into possible chemopreventive strategies (like those developed for cervical cancer).

Human Immunodeficiency Virus (HIV/AIDS)

Currently most positive patients to human immunodeficiency virus now have a longer life expectancy because of positive effect of antiretroviral therapy. However, there is an increased risk of developing some oral and non oral malignancy tumours during their lives [116]. Kaposi's sarcoma and non-Hodgkin's lymphoma have been previously known to be the most common cancers in the head and neck region among HIV positive patients, nevertheless oral squamous cell carcinoma is now being diagnosed much more frequently in HIV positive patients [117]. In one prospective, clinic-histopathological audit of infected with human immunodeficiency virus, of 200 human immunodeficiency positive patients, 8% presented with oral squamous cell carcinoma among them nine were women and seven were men with age range from 18 to 43 years and mean age of 31.7 years, the patients reported no tobacco or alcohol use and also reported not having a positive family history of cancer. The study found that the majority of the patients (62.5%) had stage III and IV disease (tumour-node-metastasis staging). There was a predilection for poorly differentiated oral squamous cell carcinoma,using Broder's histopathological classification. Oral squamous cell carcinoma associated with human immunodeficiency virus infection appears to present at a relatively young age [116]. There is limited literature of case series associating oral squamous cell carcinoma and HIV infection , there is a younger age group with median age of 40–45 years with more advanced local disease and a higher tumour stage, compared with non-HIV-positive oral SCC patients [118, 119]. Infection with the human immunodeficiencies virus (HIV) and progression to AIDS is positively correlated with malignancies of the upper aerodigestive tract, particularly Kaposi sarcoma and non-Hodgkin lymphoma and, to a lesser extent, squamous cell carcinoma (SCC) [120]. Funk and colleagues reported a very high incidence of Kaposi sarcoma in young African American males between 1985 and 1996, a time when the AIDS epidemic heavily affected that demographic population [121]. Several epidemiological studies have identified an increased risk of cancers particularly cancer of the oral cavity and lip amongst people infected with HIV, however, there is no strong evidence associating HIV infection with other head and neck cancers [117, 122-125]

Conclusion

In summary the role of genetic predisposition, previous viral infections, nutritional patterns, immunodeficiency, occupational exposure to carcinogens, socioeconomic conditions, and oral hygiene to the development of oral cancer must be deeply investigated and may help clinicians and epidermiologists to comprehensively diagnose, make a good treatment plan and help achieving good prognosis of the condition, once it is early detected. Additionally, it could be recommended for educational mobilization programs emphasizing on main determinant factors of oral cancer like high consumption of tobacco, duration of exposure to tobacco, this can also play an important role in reduction of oral cancer

incidence in young populations. Therefore early diagnosis must be focused, since this can have impact on patient's survival rate, quality of life as well treatment cost . Moreover, this can help targeting population group with maximum information spread on risk factors and preventive methods but also protective factors against oral cancers , thus multiple strategies to overcome this problem remains the primary role of treating clinicians, epidemiologists and other oral health care providers.

Acknowledgement

I am thankfully to my supervisor Professor Cao Yingguang and Professor Chen weimin for their guidance and expertise in both clinical and research dentistry. Special thanks goes to Dr. Xue Qin for sharing with me his surgical knowledge in speciality of Oral and Maxillofacial Surgery and his advise in writing this manuscript. Lastly I would like to thank my mother Musabyimana Angelique for investing so much in raising me and for her valuable love throughout my whole academic and para-academic life.

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