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A Review on the Etiology of Oral Cancer in Saudi Arabia

Abdelbaset Mohamed Elasbali[1] and Hussain Gadelkarim Ahmed[2]*

[1] College of Applied Medical Science, Al-Jouf University, Sakakah, Saudi Arabia

[2] College of Medicine, University of Hail, Hail, Saudi Arabia

**Corresponding e-mail: hussaingad5@gmail.com*

ABSTRACT

Oral cancer is one of the most common cancers worldwide. In recent years, there is a remarkable increase in the incidence of oral cancer in Saudi Arabia, particularly among relatively younger people. The increase in the incidence of oral cancer has been linked to several etiological factors, which greatly differs from geographical region to another. Therefore, the aim of the present review was to discuss the most important risk factors associated with oral cancer in light of the available literature from Saudi Arabia. Etiological factors discussed in this review of literature include genetic factors, tobacco use, alcohol consumption, infections, dietary factors, oral hygiene, etc. These etiological factors were discussed in view of the available literature (in the Medline and another electronic database) in general and literature pertains to Saudi Arabia in particular. This review can make important information available for health policymakers to implement better strategies for oral cancer prevention, early detection, and overall control. The review also helps in identifying the gaps between researchers to complete the whole image of oral cancer in Saudi Arabia with subsequent precise oral cancer control.

Keywords: Oral cancer, Etiology, Saudi Arabia, Tobacco, Alcohol, Oral hygiene

INTRODUCTION

The increasing incidence and mortality of oral cancer (the 11th commonest cancer globally) exist as a significant health problem worldwide [1]. Although there is relatively a slight decrease in the incidence of oral cancer worldwide, there is an increase in the incidence of tongue cancer. There is a wide variation in the epidemiology of oral cancer according to the geographical regions. However, in recent years there is an increase in the proportions of the younger patients in different geographical locations and mostly with tongue cancer. Oral squamous cell carcinoma (OSCC) represents the most common type of oral cancer (90%) [2].

The incidence of the cancer of the oral cavity is high in several Asian countries, particularly in the South and Southeast Asia. The wide usage of smoked, smokeless tobacco and alcohol consumption are the major predisposing risk factors for oral cancer [3]. In the Arab countries, the prevalence of oral cancer range from 1.8-2.13 per 100,000 individuals, with the majority of patients diagnosed in their 50th to 60th of their life. Relatively elevated incidence among younger people was reported in some Arab countries which were more apparent among Yemeni people (<45 years) [4].

However, several risk factors have been implicated in the etiology of oral cancer. The most important etiological factors include tobacco use (both smoked and smokeless), alcohol consumption, genetic factors, infections, dietary factors, occupational factors and others [5-8]. Therefore, the aim of the present review was to discuss the most important risk factors associated with oral cancer in light of the available literature from Saudi Arabia.

Risk Factors

Genetic factors: The cancer of the oral cavity is a multifactorial disease, which is frequently associated with genetic and epigenetic etiological factors, especially in the development of OSCC [9,10]. Tumorigenesis is usually developed from the pre-neoplastic region of genetically atypical cells, which often represent a great challenge in subsequent management. A number of dangerous genes and pathways identified to contribute to the tumorigenesis of head and neck squamous cell carcinoma (HNSCC) including TP53, CDKN2A, PI3CA and CCND1, NOTCH FBXW7, CASP8, HRAS, FAT1, TP63, and FADD [11-13]. Moreover, there are several candidate driver events genetic mutations

associated with oral carcinogenesis which includes CSMD3, CRB1, CLTCL1, OSMR and TRPM2, as well as, amplification of proto-oncogenes FOSL1, RELA, TRAF6, MDM2, FRS2, and BAG1, in addition to deletion of SMARCC1, a tumor suppressor gene. Notably, altered pathways in OSCC, such as Oncostatin-M signaling, AP-1, and C-MYB transcription networks was described in Arabian patients with tobacco-associated OSCC [14,13]. Somatic mutations of SYNE1, ROS1, and TAF1L were also reported in association with OSCC [14].

Epigenetic factors involving DNA methylation have been linked to etiology of various cancers including OSCC [15]. In most instants, the initiation and progression of the malignancy are triggered by the addition of a methyl group at the cytosine residue of CpG dinucleotide [16]. Hypermethylation of CpG usually results in the silencing of the tumor suppressor genes, while, hypomethylation results in activation of oncogenes in several malignant tumors [17,18]. OSCC associated hypermethylation-silencing have been reported in diverse genes involved in different cellular events including signaling pathways, angiogenesis, apoptosis, DNA repair, cell-cycle regulation, proliferation, and differentiation [19-23]. The hypermethylation of p16, MGMT, and DAPK gene promoters was identified in oral malignant tissues, but not in adjacent normal oral tissues [24]. Gene promoter hypermethylation in OSCC also reported a number of genes including E-cadherin, P16, P15, EDNRB, DCC, hMLH1, and KIF1A [25,26]. It was suggested that tobacco use is the possible factor that modulates the promoter hypermethylation of tumor suppressor genes through interaction with carcinogenic-metabolizing genes [27].

It was well established that microRNA plays a major role in OSCC. Several microRNA clusters have been reported in OSCC including microRNA-23b/27b, YAP1, microRNA-17-5p, microRNA-340, microRNA-92b, microRNA-17/20a, and microRNA-21 and PTEN [28-35].

An epithelial odontogenic tumor (CEOT) mutation in oncogenes and tumor suppressor genes were reported for PTEN and CDKN2A and in the oncogenes JAK3 and MET. APC, KDR, KIT, PIK3CA and TP53 missense SNVs were identified in CEOT [36].

However, there is a limited data from Saudi Arabia in this context. The study included samples of verrucous carcinoma of the oral cavity (OVC) from Saudi patients, exome sequencing showed that OVC samples lacked mutations in genes commonly associated with OSCC (TP53, NOTCH1, NOTCH2, CDKN2A, and FAT1) [37]. Another study from Saudi Arabia stated that, in addition to well-known genes of OSCC (TP53, CDKNA2, CASP8, PIK3CA, HRAS, FAT1, TP63, CCND1 and FADD) the analysis recognized a number of candidate novel driver events comprising mutations of NOTCH3, CSMD3, CRB1, CLTCL1, OSMR and TRPM2, amplification of the proto-oncogenes FOSL1, RELA, TRAF6, MDM2, FRS2 and BAG1, and deletion of the lately designated tumor suppressor SMARCC1 [13].

Tobacco Use

Tobacco smoking: Tobacco smoking plays a major role in the development of oral cancer [38]. Cigarette smoke can generate several carcinogenic groups, such as nitrosamine, benzopyrenes and aromatic amines, which was further empowered by oxidative enzymes and eventually covalently bound to DNA inducing mutation. Enzymatic or non-enzymatic metabolism of these carcinogens can generate free radicals, which can promote mutations by complex mechanisms [39]. Therefore, it was well established that the risk of developing the cancer of the oral cavity is three times higher as compared to the general population [40]. The risk of oral cancer may increase up to 87% among cigarette smokers who were exposed to involuntary smoking (environmental smoking) as compared to general population [38]. Moreover, people who quit smoking for 4 years have a 35% lower risk than those who continued to smoke [41].

Cigarette smoking can promote oral cancer through impairment of immunity, and tumor suppressor genes, such as P53 and PTEN [42-45].

Cigarette smoking is a significant public health problem in Saudi Arabia, particularly among adolescents [46]. Most studies from Saudi Arabia have shown that the prevalence of cigarette smoking among adolescent is ranging from 15% to 39.6% [47-49]. In a cross-sectional survey conducted in Jeddah (Western Saudi Arabia) to evaluate the prevalence of oral mucosal, precancerous and cancerous lesions, associated with tobacco use, cigarette smoking was found to be the most common form, followed by Shisha constituting 65.6% and 38.1% respectively, in addition to some cases accustomed to smokeless tobacco. A high prevalence (88.8%) of oral soft tissue lesions was determined [50].

However, statistic values regarding tobacco use in Saudi Arabia are much lower than the actual values, since smoking is considered as social stigma, particularly among females.

Smokeless tobacco and related substances: Smokeless tobacco consumption is increasing worldwide, leading to oral precancerous and cancerous lesions [51]. Several forms of smokeless tobacco (unburned tobacco) with different geographical names are consumed in the form of snuffing, dipping, spitting and chewing [52]. In the United States and Europe, smokeless tobacco is called snuff. In Asia, smokeless tobacco including a number of products, such as nass, naswar, khaini, mawa, mishri, gudakhu, and betel quid [53]. In Sudan and neighboring countries, smokeless tobacco with high carcinogenicity is locally known as toombak [54]. The most potent carcinogens in smokeless tobacco include tobacco-specific N-nitrosamines such as N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [53]. These products initiate the production of reactive oxygen species in smokeless tobacco resulting in fibroblast, DNA, and RNA damage in the tissues of the oral cavity. Cytochrome P450 enzymes lead to the metabolic activation, which eventually results in the formation of N-nitrosonornicotine, a major carcinogen leading to DNA damage and eventual oral cancer [51].

Shammah and khat are traditional forms of chewable tobacco commonly used in southern Saudi Arabia and Yemen [55]. Shammah is a mixture of powdered tobacco, lime, ash, black pepper, oils, and flavorings. Shammah is located in the buccal or lower labial vestibule of the mouth [56]. Several studies have established the relationship between Shammah and oral precancerous changes such as oral leukoplakia, which frequently develops into oral cancer [57-59]. The highest prevalence of oral cancer was reported to form Southern Saudi Arabia, where there was an epidemic use of Shammah [60,59].

Khat is a psychostimulant plant, commonly used chewing substances in eastern Africa and the Middle East. The khat usage is prevalent in southern Saudi Arabia, particularly Jazan region [61]. In the study from Jazan region of Saudi Arabia, the prevalence of khat usage among university students was found to be 23.1%, mostly among males (38.5%) compared to only 2.1% among females [62]. The major components of khat include cathine, cathinone, and norephedrine. These substances are structurally associated with amphetamine and noradrenaline [63].

Several studies suggested a link between khat usage and oral lesions such as hyperkeratosis and oral cancer [64-66]. Beside Shammah and khat, there are several smokeless tobacco types, which were reported to be used in Saudi Arabia including toombak, afdhal, nashoog, must, maajoon, and adani [67]. However, most of the cases of oral cancer in Saudi Arabia might be attributed to the direct or indirect effects of tobacco use.

Alcohol consumption

Alcohol consumption is estimated to account for 5% of all cancer deaths worldwide [68]. The global prevalence of alcoholic beverage consumption is high, particularly among middle-aged individuals [69]. Based on the demographic effects, the future burden of alcohol-related cancers is expected to increase to a 68% on less developed countries [68]. Several studies have shown that alcohol consumption is a risk factor for the development of oral precancerous and cancerous lesions [70-72]. Alcohol consumption and tobacco usage are responsible for up to 75% of all cases of oral cancer, particularly OSCC, which represent about 95% of all cancers of the oral cavity [73].

Alcohol induces oral cancer by enhancing the permeability of the oral epithelium, dissolving tobacco carcinogens and generation of the free radicals and acetaldehyde. These factors in most instances act together to cause DNA damage. Acetaldehyde (first ethanol's metabolite) is the most dangerous critical agent that increases the risk of OSCC. This in addition to the fact that alcohol act as synergistic agent with tobacco products to induce OSCC. Moreover, carcinogenesis of the oral tissues can be promoted by immunosuppression and malnutrition that is caused by alcohol consumption [74].

As alcoholic beverage consumption is illegal in Saudi Arabia, as well as big social stigma, particularly amongst females, that exact burden of it epidemiology remain obscure. Many studies have been conducted in this context, but all reported low epidemiological values [75-77]. Therefore, in Saudi Arabia, tobacco use and alcoholic beverage consumption will remain a real challenge that requires particular public health policies.

Infections

Human papillomavirus (HPV): HPV is the commonest virus that is associated with several cancers including oral cancer [78]. The prevalence of HPV is greatly varied across the globe [79]. HPV was found to cause a distinct subset

of OSCC with unique epidemiological, clinical and molecular features which differ from non-HPV associated OSCC [80]. However, with the increasing tobacco control efforts, the incidence of HPV related OSCC seems to be rising, particularly in HPV-epidemic areas. P16 (tumor suppressor gene), which regulate cell cycle, is comprehensively used as a surrogate marker for HPV infection. Upon infection with HPV high risk (HR-HPV) types (HR-HPV 16, 18, 31, 33 ,34, 35, 39, 51, 52, 56, 58, 59, 66, 68, and 70), p16 is aberrantly overexpressed [81]. HR-HPV subtypes 16 and 18 are the most common types associated with OSCC [82,83].

Data on the prevalence of HPV, survival of infected patients, and mortality rate are scarce in Saudi Arabia [84]. The available data on HPV epidemiology are related to cervical infections which vary from 9.8% to 43% with most frequent subtypes 16 and 18 [85,86]. During our search, we didn't find any report from Saudi Arabia discussing the relationship between HPV and oral cancer.

Epstein-Barr virus (EBV): EBV is a human herpes virus which infects relatively all adults and is linked to a number of human diseases including mononucleosis and several cancers including head and neck cancers (HNCs) [87,88]. In addition to the well-known risk factors, EBV plays an important role in the etiology of OSCC [89,90]. The prevalence of EBV is associated with OSCC and appears to be boosted by some forms of smokeless tobacco [89].

However, there are limited studies from Saudi Arabia investigating the relationship between EBV and oral cancer. In the study to identify genetic aberrations driving OSCC development among users of Shammah, there was a tendency for increased mutations, amplifications and driver events in samples with a history of Shammah exposure particularly those that tested EBV positive, suggesting an interaction between tobacco exposure and EBV [91]. Another study investigated the samples obtained from Saudi patients with nasopharyngeal carcinoma to detect EBV and P53 mutation, about 92% of the tumor specimens were found to harbor EBV DNA [92].

Furthermore, there are other viruses suggested having a role in the etiology of oral cancer. Herpes simplex virus was found to induce a number of mutations in cells. Herpes simplex 6 was found to be capable of transforming cells to a malignant phenotype. Immunodeficiency virus was found in patients with hairy leukoplakia [93].

Bacterial infection: The role of bacteria in the etiology of oral cancer is gaining a growing interest in recent years. The oral cavity is inhibited by many of the bacterial species. Some of them have a key role in the development of the oral disease. The association between the oral microbiome and systemic diseases such as HNCs is getting appreciated interests. Developing evidence suggest the association between periodontal disease and oral cancer. This is suggested to be through chronic inflammation, which is a major factor in both diseases, however, no such reports were found in Saudi Arabia. [94, 95].

Fungal: Oral epithelium tissues are exposed to a number of microbes, including commensal fungi [96]. The most frequent encountered fungi are *Candida* species, which is responsible for significant oral problems for both immunocompromised and immunocompetent individuals [97].

Since the initial reports of an association between candidiasis with oral pre-cancer and cancer, various theories have been debated regarding the role of *Candida* in the development and transformation of oral pre-malignancies [98]. It was suggested that the intense inflammatory events induced by the interaction between *Candida* and mucosal epithelium tissues play an important role in the carcinogenesis [96]. Also, it was suggested that *Candida* along with other co-factors may play a role in initiation and promotion of carcinogenesis, however, no such reports were found in Saudi Arabia [98].

Dietary Factors

Diet and inflammation have been proposed to be significant risk factors for the cancer of the oral cavity. The pro-inflammatory potential of the diet, as presented by higher DII scores (i.e., with a more pro-inflammatory diet), is linked to higher odds of oral cancer [99]. Beside tobacco use and alcohol consumption, there are several dietary types suggested increasing the risk of oral cancer, such as high intake of red and processed meat [100,101]. On the other hand, high intake of fresh vegetables, fruits, fish and seafood usually associated with decreased risk of oral cancer, however, no such reports were found in Saudi Arabia [102-104].

Occupational Factors

Several occupational subsets are linked to the etiology of oral cancer. Dentists are proposed to have increased risk of tongue cancer. Occupations associated with increased exposure to tobacco products, alcohol consumption or HPV

infections have a higher risk of developing oral cancer due to occupational chemical exposures [105]. In a case-control study, the role of occupations and occupational exposures as risk factors for OSCC was investigated. A significantly increased risk was found for pulp industry workers, and wood or product workers. This increased risk may be due to the exposure to chemicals such as phenoxyacetic acids, however, no such reports were found in Saudi Arabia [106].

Oral Hygiene Related Factors

Several studies have established the association between oral hygiene and periodontal disease with elevated risk of carcinoma of head and neck [107,108]. A study was examined the association between oral hygiene and head and neck cancer (HNC) and whether this association differed by the consumption of alcohol, betel quid, or cigarette and by the genetic polymorphisms of inflammation-related genes. A positive association between poor oral hygiene and HNC appeared to differ by alcohol or cigarette consumption and the genotypes of IL6 rs1800796 [109]. Gum bleeding, no dental care, and daily mouthwash use were factors associated with oral cancer regardless of tobacco and alcohol consumption [110]. Another study found that poor oral hygiene due to infrequent tooth brushing and sores caused by dentures are risk factors for oral cancer, however, no such reports were found in Saudi Arabia [111].

CONCLUSION

Tobacco use may be the most evidenced factor that contributes to the risk of oral cancer in Saudi Arabia. Cigarette smoking and Shammah usage may be the most prominent factors. The exact association between oral cancer and many other risk factors still need a lot of research. Public education and awareness about the causes of oral cancer, particularly tobacco use are urgently needed in Saudi Arabia

DECLARATIONS

Conflict of Interest

The authors have disclosed no conflict of interest, financial or otherwise.

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