Aetiology of Oral Cancer in the Sudan

Hussain Gadelkarim Ahmed[1]

[1]Department of Pathology, College of Medicine, University of Hail, KSA, University of Khartoum, Sudan.

Corresponding Author:
Hussain Gadelkarim Ahmed
Department of Pathology, College of Medicine, University of Hail
Saudi Arabia
E-mail: hussaingad1972@yahoo.com; he.ahmed@uoh.edu.sa

ABSTRACT

Objectives: To review the studied risk factors that linked to aetiology of oral cancer in the Sudan. There have been numerous reports in the increase in the incidence of oral cancer from various parts of the world. A recent trend for a rising incidence of oral cancer, with the absence of the well established risk factors, has raised concern. Although, there are inconsistent data on incidence and demographical factors, studies suggest that the physiologic response to risk factors by men and women vary in different populations.
Material and Methods: This review principally examines 33 publications devoted to aetiology of oral cancer in the Sudan, in addition to some risk factors that are commonly practiced in the Sudan.
Results: Several studies examining risk factors for oral cancer include tobacco use (Smoked and Smokeless), alcohol consumption, occupational risk, familial risk, immune deficits, virus infection and genetic factors.
Conclusions: Toombak use and infection with high risk Human Papilloma Virus (HPV) were extensively investigated and linked to the aetiology of oral cancer in Sudan.

Keywords: oral cancer; DNA Probes, HPV; nicotine; tobacco; etiology.

Accepted for publication: 22 April 2013
To cite this article:
Ahmed HG. Mandibular Aetiology of Oral Cancer in the Sudan.
URL: http://www.ejomr.org/JOMR/archives/2013/2/e3/v4n2e3ht.pdf
doi: 10.5037/jomr.2013.4203

INTRODUCTION

The incidence rates of oral cancer are 3.7% for men and 2.6% for women in the Sudan [1]. Several lifestyle risk factors for the development of oral cancer are familiar, including tobacco products, alcohol, infections, dietary factors, chemical irritants and frank carcinogens. Prevalence of oral cancer is 3.2% in Sudan and the disease is mainly attributed to N-nitrosamine rich oral snuff consumption [1].

There are mainly 4 smokeless tobacco products: loose leaf or chewing tobacco, snuff, plug tobacco and twist or roll tobacco. Chewing tobacco and snuff are by far the most widely distributed types of smokeless tobacco. Initially, snuff was used for nasal application (sniffing). However, snuff is now habitually used orally by insertion it between lower gum and cheek or lip (dipping) [2,3].

The oral use of snuff in North America and Western Europe is causally associated with an increased risk for cancer of the oral cavity and pharynx. Snuff dipping has also been incriminated as being associated with cancer of the nasal cavity, oesophagus, pancreas, kidney and urinary bladder [2-6], and other pre-neoplastic changes such as leukoplakia [2,3].

However, all these risk factors are beyond the scope of the present review. The main goal of this paper was to review the studied risk factors that linked to aetiology of oral cancer in Sudan.

MATERIAL AND METHODS

In this review 33 studies published up to August 2012 in the aetiology of oral cancer from Sudan were included. They were identified through searches of the MEDLINE database, using the keywords: ‘‘Sudan”, ‘‘Toombak”, ‘‘infection”, ‘‘HPV”, ‘‘Oral hygiene”, ‘Alcohol”, Hot meals”, “Cancer”, “Oral squamous cell carcinoma” and ‘‘risk factors”. Papers were also searched among those quoted as references in the retrieved studies, as well as, in a few previous reviews. Only papers in English were considered.

RESULTS

Risk factors

Toombak

In the Sudan, oral snuff, known locally as toombak, is home-made from finely ground leaves of *Nicotiana rustica*, a tobacco species with a particularly high content of nicotine and minor alkaloids. This tobacco is mixed with Natron or atron (sodium bicarbonate) (about 4:1), then water is added to the mixture, and after a period of about 2 hours or longer the mixture, called “saffa” [7].

Natron: Natron or atron (sodium bicarbonate ($Na_2H(CO_3)_2.2H_2O$). Atron, opposed to lime in other parts of the world, is probably added to toombak for its alkaline effects. It has been shown that at high pH (11.0 - 11.8) nicotine is completely protonated and its rate of absorption is increased [8,9]. Atron probably quickens absorption of nicotine from toombak to the central nervous system [10].

N-nitrosamines: the study by Idris et al. [8] have analyzed the Tobacco Specific Nittrose Amine (TSNA) levels in toombak and found unusually high levels of these TSNAs compared to the reported levels in any snuff [8,11,12]. These high levels of TSNAs found in toombak were partially attributed to the use of tobacco Species, *Nicotiana rustica*, and fermentation of toombak at elevated temperature, prolonged storage, and contamination during processing [13-15]. Therefore, assuming chronic toombak use, the minimum daily dose of NNK to which these users were exposed was 0.12 - 0.44 mg. This is the highest documented uptake of a non occupational carcinogen [16].

Epidemiological evidence suggests that toombak is a risk factor for cancer of the oral cavity and possibly of the oesophagus in the Sudan [17-19]. Data from 1,916 cases of oral neoplasms occurring in the Sudan in a 16-year period, from January 1970 to December 1985, were retrieved and analyzed. The study revealed a relatively high frequency of oral neoplasms in comparison with neighbouring countries. Squamous-cell carcinoma was the most common oral malignancy (66.5%), followed by tumours of the salivary gland (14.7%), neoplasms of non-odontogenic and non-epithelial origin (9.6%) and odontogenic neoplasms (8.6%). Men had a higher frequency than women [7]. Female toombak use is considered social stigma in Sudan, consequently the 95% of toombak users were males, which supports its etiological effects.

In Sweden, snus (locally known as snus), was introduced since the year 1637. The study by Idris et al. [8] compared between snus (Sweden) and Toombak. Snus and toombak dippers develop a clinically and histologically characteristic lesion at the site of dipping. Snus was associated with a lower risk of cancer of the oral cavity (relative risk: RR 5-6-fold) compared to high risk of toombak (RR 7.3-73.0-fold) [20].

Clinical (n = 281) and histopathological (n = 141) characteristics of toombak-associated oral mucosal lesions detected in an epidemiological study in northern Sudan in 1992/93 found Parakeratosis, pale surface staining of the epithelium and basal cell hyperplasia were commonly observed, but epithelial dysplasia

was infrequent (10/141) [21]. Ultra structural features oral toombak dipper's lesions with distinctive sub epithelial hyaline deposits their bulk is made up of collagen, as typical cross-striated fibrils. The pathogenesis of this deposit could therefore be interpreted as over-production and/or reduced turnover of collagen by resident fibroblasts, which is further altered by the ingredients of toombak [22].

In a study investigated the effects of toombak on primary normal human oral keratinocytes, fibroblasts, and a dysplastic oral keratinocytic cell line, compare to Swedish snuff, a potential for toombak, higher than for Swedish snuff, to damage human oral epithelium [23]. Furthermore, In OSCC, apoptosis was associated with bax expression and was unaffected by p53 gene status or toombak use in OSCC from the Sudan [24].

The study by Ibrahim et al. [25] analyzed 14 oral squamous-cell carcinomas (OSCCs) and 8 pre-malignant oral lesions from different Sudanese patients for prevalence of mutations in exons 5 to 9 of the p53 gene in relation to toombak-dipping status. OSCCs (14 from Sudan, 28 from Scandinavia), and 3 pre-malignant oral lesions from Sudanese non-dippers were used as controls. A statistically significant ($P < 0.05$) increased incidence in mutations of the p53 gene was found in OSCCs from toombak dippers (93%; 13/14), as compared with those from non-dippers in Sudan (57%; 8/14) and in Scandinavia (61%; 17/28) respectively [25].

Several studies from Sudan have proved that toombak use is a major risk factor that responsible of high frequencies of potential malignant oral lesions and oral cancers and in particular OSCCs in the Sudan. Most of tumours were observed at the site of dip application (lower lip). Oral cancer seems to be gender-specific, as the majority of cases were males [26-31].

However, all of the preceded discussed literatures support the criminal role of toombak in the aetiology of oral cancer in the Sudan. Probably toombak has a major role but it is not alone responsible of oral cancer in the Sudan, particularly in the recent years with dramatic increase in overall cancer risk.

Tobacco smoking

Most oral cancer cases and deaths are due to both individual predisposition, linked to specific genetic characteristics, and exposure to carcinogens, caused by lifestyle behaviours, particularly tobacco [32].

Nicotine is only a minor component of tobacco leaves and constitutes about 5% of the total weight of dry plant leaves. This substance is the main psychoactive alkaloid of tobacco. When tobacco smoke is inhaled, 25% of the nicotine reaches the brain in about seven seconds. Nicotine functions by binding to nicotinic acetylcholine receptors, causing increased heart rate, vasoconstriction, and alertness [33]. Nicotine induces dependence among genetically, mentally and socially predisposed individuals with addictive personalities [34,35].

Tobacco carcinogenicity is more than evident and about one fourth of oral cancer cases are attributable to cigarette smoking [36]. Specifically, tobacco products are causally linked to a variety of cancers, including those of the lung, oral cavity, nasal cavity, larynx, oropharynx, hypopharynx, oesophagus, stomach, liver, pancreas, bladder, ureter, kidney, cervix, and myeloid leukaemia.

More than 60 carcinogens are present in cigarette smoke and at least 16 in unburned tobacco have been identified. The most important are tobacco-specific nitrosamines, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN), polycyclic aromatic hydrocarbons (PAH), such as benzopyrene, and aromatic amines. In particular, NNK, NNN and PAH have been causally linked to oral cancer. The activity of carcinogens is generally exerted through DNA adducts [37,38].

Few women admit to tobacco use due to cultural norms in the society, and among males the estimated prevalence is around 20% [39]. In most samples from indoor air polluted with environmental tobacco smoke (ETS), the highest concentration of an individual TSNA is that of NNK. When nonsmokers had remained for up to 2 hours in a test laboratory with high ETS pollution, they excreted measurable amounts of NNK metabolites in the urine, indicative of the uptake of TSNA [40].

A house to house cross-sectional survey of a random population sample of 4,535 households was performed, as the first survey on tobacco in the Sudan. Of the 23,367 household members identified, 21,648 (92.6%) eligible individuals were questioned about tobacco use. Results showed that, among children and adolescents (4 - 17 years) prevalence of tobacco use was quite low (2%, range 1 - 2%), but there was an abrupt increase up to 25% in late adolescence. Among the adult population aged 18 years and older the prevalences of toombak use (34%) and cigarette smoking (12%) among males were significantly higher than among females (2.5 and 0.9%, respectively) [39].

As part of the development of a screening procedure for oral cancer and precancer, exfoliative cytology (EFC) was applied to a retrospective cohort to assess the presence and severity of oral epithelial atypia (ET) in 300 subjects (100 toombak dippers; 100 cigarette smokers; 100 non-tobacco users) without prior knowledge of the subjects' tobacco exposure. ET was ascertained in 29 subjects and could not be ascertained in the remaining

271. Among the 29 subjects with ET, there were 11 (38%) toombak dippers, 14 (48%) cigarette smokers and 4 (14%) non-tobacco users. Among the 271 subjects without ET, there were 89 (33%) toombak dippers, 86 (32%) cigarette smokers and 96 (35%) non-tobacco users. For the ET among toombak dippers and cigarette smokers, adjusted OR and the 95% CI were found to be 3 (0.91 - 9.7) and 4 (1.2 - 12.3), respectively [26].

Both in tobacco smoke and smokeless tobacco, carcinogenic N-nitroso compounds (NOC) are implicated as DNA-damaging agents in cancers of the aerodigestive tract and the pancreas. Poor oral hygiene was found to contribute to the formation of nitrosamines in the oral cavity. The evidence so far accumulated demonstrates that tobacco habits increase endogenous NOC formation, thus adding to the burden of exposure by preformed carcinogenic NOC in tobacco products [41].

However, in view of these studies, smoked tobacco has a role in aetiology of oral cancer, but how far this is contributing in oral cancer in Sudan and how far it is significant is unknown, since there is lack of data in this context.

Alcoholic drinks

Alcoholic beverages are a heterogeneous group of beverages, with variable number, type and concentration of components. The common components are ethanol and water. Carbon dioxide, minerals (mostly potassium, phosphates and sodium), amino-acids, organic and inorganic acids, polyphenols and carbohydrates are prevailing in beers. Alcohols, carbohydrates (mainly sugar and pectin), organic acids, minerals (mostly potassium, iron, phosphates and calcium), polyphenols, vitamins and carbon dioxide are the major wine components, while spirit and liqueur composition is very assorted, with common components being alcohols, acids (mainly fatty and acetic acid), esters, aldehydes, terpenes, ethereal oils and volatile bases [42,43].

Regular alcohol consumption is associated with an increased risk for oral cancer. Such association is dose-dependent. Indeed, among individuals consuming 4 - 5 drinks daily, the risk for cancer of the oral cavity is 2 - 3 folds higher than among non-drinkers [44-47].

Overall, 7 - 19% oral cancer cases are attributable to heavy alcohol drinking [36,48]. Oral cancer risk among alcohol drinkers further increases for tobacco chewing or smoking [49]. The major alcohol metabolising enzymes are alcohol dehydrogenase, that oxidises ethanol to acetaldehyde, and aldehyde dehydrogenase, that detoxifies acetaldehyde to acetate. Acetaldehyde is responsible for the oral carcinogenic effect of ethanol, owing to its multiple mutagenic effects on DNA [44,46].

In addition, ethanol is not the only carcinogen present in alcoholic drinks, other minor components, such as nitrosamines, acrylamide, oxidized polyphenols are classified as probable carcinogenic to humans, with animal experiments showing mutagenic activity on oral epithelial cells [50].

Since alcohol consumption is considered illegal in Sudan, no available data about the relationship between alcoholic beverage consumption and oral cancerous development. However, there is only one Sudanese study published in this context. The study evaluated cytological atypical changes in apparently healthy oral mucosa exposed to smoking, alcohol, hot meals, and peppers. The features of cytological atypia were verified among 10 individuals, including 5 smokers, 2 alcohol users, 2 hot meals and peppers consumers, and one non-exposed. For atypia among tobacco smokers, the adjusted Odds Ratio (OR) and the 95% CI were found to be 2 (0.246 - 16.24). Increased keratinisation was detected among 27 (45%) of the smokers ($P < 0.0001$), 17 (32.7%) of the pepper and hot meals consumers ($P < 0.005$), 4 (11.8%) of the alcohol consumers, and among 2 (3.7%) of the non-exposed group. Statistical analyses revealed a greater mean number of AgNORs per nucleus in smokers (3.68) followed by (2.82) alcohol consumers, compared to the habitual peppers and hot meal consumers (2.28) and the non-exposed group (2.00) [51].

However, no available data about alcoholic consumers in the Sudan, approximately 95% of the habitual use to drink in hide, since it is considered as illegal and social stigma. Consequently, nobody can estimated or even imagine its burden as a risk contributes to the aetiology of oral cancer in the Sudan.

Human papilloma viruses (HPV) infection

The HPV are a large family of non-enveloped DNA viruses, mainly associated with cervical cancers. Recent epidemiologic evidence has suggested that HPV may be an independent risk factor for oropharyngeal cancers [52]. HPV has a wide disease spectrum affecting the cutaneous and mucosal areas of the body, ranging from benign common warts to invasive carcinoma. HPV infections have been reported in a number of body sites, including the anogenital tract, urethra, skin, larynx, tracheobronchial mucosa, nasal cavity, paranasal sinus, and oral cavity [53,54]. Oral HPV infection may be associated with different diseases of oral cavities. HPV is one of the most prevalent infections in the world with several new cases diagnosed every year [55].

HPVs are small DNA viruses with about 7900 nucleotide bases long [53]. There are more than 120 genetically different, yet closely related HPVs that are referred to

as genotypes. By definition, each type is defined by having less than 90% DNA base pair homology with any other identified HPV type. The genotypes are numbered in the order of their discovery [56].

The HPV genome encodes DNA sequences for six early (E1, E2, E4, E5, E6, and E7) proteins associated with viral gene regulation and cell transformation, two late (L1 and L2) proteins which form the shell of the virus, and one region of regulatory DNA sequences. The different HPV types are characterized by genotypic variations in the DNA base-sequences of E6 and E7. It is these genotypic differences that permit stratification of the virus oncogenic phenotype into high, intermediate-, and low-risk types [55].

In the case of high-risk HPV infection and under favourable conditions, the viral genome is integrated into the host genome, which is the necessary event for the keratinocytes immortality. During this process of integration, the circular form of viral genome breaks at the level of the E1 and E2 regions, never at the level of the E6 or E7 region. Different studies have shown that the integrated part of the genome corresponds to E1, E6, and E7, while the regions from E2 to E5 are lost and are not transcribed in the tumours. The loss of E2 during this process of integration produces the loss of E6 and E7 control. Therefore, the sequences E6 and E7 are directly involved in the cellular cycle by inhibiting the normal functions of p53 and pRb, respectively. The protein p53 is known as the "genome's guard" and in the case of DNA damage, the p53 can provoke the arrest of cellular division and assure the time necessary for DNA repair. If damage cannot be repaired, p53 is able to induce the programmed cellular death and prevent the propagation of DNA damage in subsequent generations of cells. In the case of other types of tumours, p53 is usually mutated and acts as a real *oncogene*. In the case of HPV infection, E6 suppresses the properties of p53 gene product, achieving the functional equivalent of the two hits required to knock out both alleles of a tumour suppressor gene. The mutations of *p53* are normally not found. The E7 protein interacts with retinoblastoma protein (pRb), which is the crucial factor for the cellular cycle control. This interaction causes the release of the transcription factor E2F, which is now free to act and can stimulate the cellular division. E7 is also able to bind and inactivate the protein kinase inhibitors p21 and p27 and can interact with different proteins whose significance has still not been determined [55,57]. HPV has gained much interest recently, because it is accepted as important correlates of cervical cancer. Oral HPV infections have not been studied to the degree as those of the genital tract, although the evidence of association between certain tumours and HPV infection today is indisputable. Oncogenic HPVs are associated with oral malignancies, but its prevalence varies widely in different studies. Although study results are mixed, it seems possible that smoking and alcohol use may interact with HPV infection to increase a person's risk of oral cancer. So, oral HPV infections need to be studied and investigated deeply so that it can guide us for future cancer prevention programs, including oral HPV vaccination for oral HPV infections.

Nevertheless, few studies have investigated the role of viruses in general and HPV in particularly in the aetiology of oral cancer in the Sudan. The first study investigated potentially malignant oral mucosal lesions from Sudanese patients (9 hyperplasias/40 dysplasias). HPV was found in only 2 Sudanese cases, both of which harboured both type 6 and type 11: both these cases demonstrated mild epithelial dysplasia [58]. Another study from Sudan investigated a total of 40 cases (patients with OSCCs) and 15 controls (patients with benign lesions) were included in the study. The cases included; carcinomas of the oral cavity proper, carcinomas of the lip vermilion. HPV was detected among 6 (15%) of the cases, four were HPV type 16 and two were HPV type 18 [59]. A recent study from Sudan reported the presence of HPV in head and neck cancers (HNCs) in general and in oral in particular. The study was performed on 150 samples of patients diagnosed with HNSCs. Six of the 150 (4%) HNSCCs were HPV positive. HPV16 was the most prevalent type, with single infections present in 3/6 (50%) cases, whereas HPV18 and HPV33 were detected in 2/6 (33%) and 1/6 (17%), respectively. HPV infections were detected in 3 (50%) cases of oral cavity and 3 (50%) cases of pharynx [60].

Furthermore, very limited studies have investigated the role of other viruses such as, Epstein-Barr virus (EBV) and Herpes Simplex Virus (HSV) in the aetiology of oral cancer in Sudan beside HPV. Using PCR/DNA sequencing, a study has investigated the prevalence of HPV, HSV and EBV DNA in brush biopsies obtained from 150 Sudanese toombak dippers and 25 non-toombak dippers in formalin-fixed paraffin-embedded tissue samples obtained from 31 patients with oral dysplasias (25 toombak users and 6 non-users), and from 217 patients with oral cancers (145 toombak users and 72 non-users). In the brush tissue samples from toombak users, HPV was detected in 60 (40%), HSV in 44 (29%) and EBV in 97 (65%) of the samples. The corresponding figures for the 25 samples from non-users were 17 (68%) positive for HPV, 6 (24%) positive for HSV and 21 (84%) for EBV. The formalin-fixed samples with oral dysplasias were all negative for HPV. In the 145 oral cancer samples from toombak users, HPV was detected in 39 (27%), HSV in 15 (10%) and EBV in 53 (37%) of the samples. The corresponding

figures for the samples from non-users were 15 (21%) positive for HPV, 5 (7%) for HSV and 16 (22%) for EBV. These findings illustrate that prevalence of HSV, HPV and EBV infections are common and may influence oral health and cancer development. These observations warrant further studies involving toombak-associated oral lesions, to uncover the possible mechanisms of these viral infections in the development of oral cancer, and the influence of toombak on these viruses [61]. In another study investigated the prevalence of HPV, HSV and EBV in 155 OSCCs from eight different countries from different ethnic groups, continents and with different socioeconomic backgrounds, the highest prevalence of HPV was seen in Sudan (65%) [62].

Genetic factors

Genetic factors have enhancing roles in many cancers including oral cancer. Limited studies have dealt with the investigation of association between genetic factors and level of risk for development of oral cancer in Sudan. In a study aiming to explore possible range of gene expression profiles in head and neck squamous cell carcinomas (HNSCC) and pair wised normal controls from Sudanese (n = 72) and Norwegian (n = 45) patients using a 15K cDNA microarray and to correlate the findings with clinicopathologic variables. Differences in gene expression between tumour and nontumour tissues were identified in HNSCCs. Analysis of the two population groups revealed a common set of 73 genes within three main biological pathways. This indicates that the development of HNSCCs is mediated by similar biological pathways regardless of differences related to race, ethnicity, lifestyle, and/or exposure to environmental carcinogens. Of particular interest, however, was the valuable association of gene expression signature found with toombak use and anatomic site of the tumours [63].

The prevalence of mutations in exons 2 and 3 of the S100A4 gene was analyzed in the 14 OSCCs from toombak-dippers and in 25 cases of OSCCs from the control non-snuff-dippers. Of the 14 OSCCs investigated from toombak-dippers, mutations in the p21waf1 exon 2 were found in 43% (6 out of 14), compared to 14% (2 out of 14), 22% (6 out of 27) and 14% (5 out of 35) found in those from non-snuff-dippers from the Sudan, Scandinavia and the USA/UK, respectively [64]. The study by Lazarus et al. [65] suggested that toombak components such as TSNAs may induce p53 mutations in head and neck SCCs and are likely contributors to the tobacco-induced carcinogenic load in humans.

A recent study investigated the prevalence of p53 codon 72 polymorphism in brush biopsies obtained from a Sudanese population. A total of 174 individuals were included in the study; chronic toombak users (n = 152) and non-users (n = 22). DNA was extracted from all the samples and genotyped for the codon 72 polymorphism by polymerase chain reaction/restriction fragment length polymorphism. The Arg/Pro genotype was found in 53% of the 174 study participants, compared to 21% found with Arg/Arg and 26% found with Pro/Pro. Stratifying by toombak use, 28 (18%), 45 (29%) and 79 (52%) of the 152 samples from toombak users had Arg/Arg, Pro/Pro and Arg/Pro respectively, compared to 9 (41%), 0 (0%) and 13 (59%) found in the 22 samples from non users. The differences between the samples from toombak users and non users in Arg/Arg and Pro/Pro codon 72 polymorphism and HPV infection were statistically significant ($P < 0.05$). The study indicated that a high prevalence of the genotype Arg/Pro at the p53 codon 72 may contribute to susceptibility to OSCC, especially in combination with the use of carcinogenic tobacco-specific nitrosamine (TSNA)-rich toombak [66]. In another study, 9 genes related to apoptosis, cell cycle regulation and intermediate filament proteins were selected and their differential expression status was examined by real-time quantitative RT-PCR in 26 samples of Sudanese OSCCs and their matched normal controls. The findings were correlated with the habit of toombak use. The mRNA levels of Bcl2, keratin 1, keratin 13 and p53 were significantly lower and the level of survivin was significantly higher in the OSCC samples of the toombak users compared to their paired control samples. A significant down-regulation in keratin 1 and keratin 13 expression levels was found in the OSCC samples of the non-toombak users compared to their normal control samples. The differential expression of genes related to apoptosis, cell cycle regulation and types I and II keratin could be useful diagnostic markers and provide valuable information for the understanding of oral malignancy in relation to toombak use [67].

Other factors

Besides tobacco and alcohol, other risk factors have been studied in relation to oral cancer in Sudan. Among these factors, diet and nutrition have been suggested to play an important role [68]. So far there is a lack of studies focusing on the prevalence of a wide spectrum of oral mucosal lesions (OML) in patients with dermatologic diseases. This is noteworthy as skin lesions are strongly associated with oral lesions and could easily be neglected by dentists. A study from Sudan found that OML were frequently diagnosed in skin diseased patients and varied systematically with age, gender, systemic condition and use of toombak [69].

Epidemiological studies conducted in various populations reported an inverse association between intake of fruit and vegetables and the risk of cancer of the oral cavity [70]. Thus, fruit and vegetables appear to be the most consistent favourable dietary aspect on oral and pharyngeal neoplasm. In a network of studies from Italy, about 20 - 25% of cancers of the oral cavity and pharynx were attributed to low fruit and vegetable consumption, and the population attributable risk, rose to 85 - 95% when tobacco and alcohol consumption were also considered [71].

The evidence on the role of milk and dairy products, as well as coffee and tea, on the risk of cancer of the oral cavity and pharynx is scanty, and does not indicate any consistent association [69]. Meat consumption has been related to an increased risk of oral cancer [72]. However, none of these factors has been investigated in the Sudan. As Sudan is very large country with different climates, there is an enormous diversity of exposures to these factors.

CONCLUSIONS

Toombak plays a major role in the aetiology of oral cancer in Sudan, since it is a potent carcinogenic, as well as it acts as a synergistic factor enhances the carcinogenesis of other etiological factors, such as genetic factors and viruses. The role of Human Papilloma Virus in aetiology of oral cancer is reasonable, but the question how far is it without toombak? The real contribution of other risk factors such as viruses other than Human Papilloma Virus, smoked tobacco and alcohol still need more investigation other factors that have increased risk or reverse risk need more investigation.

AKNOWLEDGEMENT AND DISCLOSURE STATEMENTS

The author report no conflict of interest related to the present study.

REFERENCES

1. International Agency for research on cancer: GLOBOCAN 2008. Available from: http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900#MEN
2. Tobacco habits other than smoking. IARC Monogr Eval Carcinog Risk Chem Hum. 1985 Sep;37:37-136. Review. [Medline: 3910553]
3. Cullen JW, Blot W, Henningfield J, Boyd G, Mecklenburg R, Massey MM. Health consequences of using smokeless tobacco: summary of the Advisory Committee's report to the Surgeon General. Public Health Rep. 1986 Jul-Aug;101(4):355-73. Review. [Medline: 3090602] [FREE Full Text]
4. Brinton LA, Blot WJ, Becker JA, Winn DM, Browder JP, Farmer JC Jr, Fraumeni JF Jr. A case-control study of cancers of the nasal cavity and paranasal sinuses. Am J Epidemiol. 1984 Jun;119(6):896-906. [Medline: 6731431]
5. Kabat GC, Dieck GS, Wynder EL. Bladder cancer in nonsmokers. Cancer. 1986 Jan 15;57(2):362-7. [Medline: 3942969]
6. Higginson J, Oettle AG. Cancer incidence in the Bantu and "Cape Colored" races of South Africa: report of a cancer survey in the Transvaal (1953-55). J Natl Cancer Inst. 1960 Mar;24:589-671. [Medline: 14401758]
7. Idris AM, Ahmed HM, Mukhtar BI, Gadir AF, el-Beshir EI. Descriptive epidemiology of oral neoplasms in Sudan 1970-1985 and the role of toombak. Int J Cancer. 1995 Apr 10;61(2):155-8. [Medline: 7705940] [doi: 10.1002/ijc.2910610202]
8. Idris AM, Nair J, Ohshima H, Friesen M, Brouet I, Faustman EM, Bartsch H. Unusually high levels of carcinogenic tobacco-specific nitrosamines in Sudan snuff (toombak). Carcinogenesis. 1991 Jun;12(6):1115-8. [Medline: 2044192] [doi: 10.1093/carcin/12.6.1115]
9. Brunnemann KD, Hoffmann D. The pH of tobacco smoke. Food Cosmet Toxicol. 1974 Feb;12(1):115-24. [Medline: 4459223] [doi: 10.1016/0015-6264(74)90327-7]
10. Brunnemann KD, Genoble L, Hoffmann D. N-Nitrosamines in chewing tobacco: an international comparison. J. Agric. Food Chem. 1985;33:1178-81. [doi: 10.1021/jf00066a039]
11. Idris AM, Nair J, Friesen M, Ohshima H, Brouet I, Faustman EM, Bartsch H. Carcinogenic tobacco-specific nitrosamines are present at unusually high levels in the saliva of oral snuff users in Sudan. Carcinogenesis. 1992 Jun;13(6):1001-5. [Medline: 1600602] [doi: 10.1093/carcin/13.6.1001]
12. Tso TC. Physiology and Biochemistry of Tobacco Plants. Stroudsburg, PA: Dowden, Hutchinson and Ross; 1972. p. 393.
13. Andersen RA, Burton HR, Fleming PD, Hamilton-Kemp TR. Effect of storage conditions on nitrosated, acylated, and oxidized pyridine alkaloid derivatives in smokeless tobacco products. Cancer Res. 1989 Nov 1;49(21):5895-900. [Medline: 2790803] [FREE Full Text]
14. Djordjevic MV, Fan J, Bush LP, Brunnemann KD, Hofmann D. Effects of storage conditions on levels of tobacco specific N nitrosamines and N nitrosaminoacids in U.S. moist snuff. J Agr Food Chem 1993. 11:1790-4. [doi: 10.1021/jf00034a051]
15. Prokopczyk B, Wu M, Cox JE, Hoffmann D. Bioavailability of tobacco-specific N-nitrosamines to the snuff dipper. Carcinogenesis. 1992 May;13(5):863-6. [Medline: 1587000] [doi: 10.1093/carcin/13.5.863]

16. Murphy SE, Carmella SG, Idris AM, Hoffmann D. Uptake and metabolism of carcinogenic levels of tobacco-specific nitrosamines by Sudanese snuff dippers. Cancer Epidemiol Biomarkers Prev. 1994 Jul-Aug;3(5):423-8. [Medline: 7920210] [FREE Full Text]
17. Elbeshir EI, Abeen HA, Idris AM, Abbas K. Snuff dipping and oral cancer in Sudan: a retrospective study. Br J Oral Maxillofac Surg. 1989 Jun;27(3):243-8. [Medline: 274281]
18. Babekir AR, el Fahal AH, Alla AH. Oesophageal cancer in Sudan. Trop Doct. 1989 Jan;19(1):33-4. [Medline: 2922814]
19. Idris AM, Ahmed HM, Malik MO. Toombak dipping and cancer of the oral cavity in the Sudan: a case-control study. Int J Cancer. 1995 Nov 15;63(4):477-80. [Medline: 7591252] [doi: 10.1002/ijc.2910630402]
20. Idris AM, Ibrahim SO, Vasstrand EN, Johannessen AC, Lillehaug JR, Magnusson B, Wallström M, Hirsch JM, Nilsen R. The Swedish snus and the Sudanese toombak: are they different? Oral Oncol. 1998 Nov;34(6):558-66. Review. [Medline: 9930371] [doi: 10.1016/S1368-8375(98)00047-5]
21. Idris AM, Warnakulasuriya KA, Ibrahim YE, Nielsen R, Cooper D, Johnson NW. Toombak-associated oral mucosal lesions in Sudanese show a low prevalence of epithelial dysplasia. J Oral Pathol Med. 1996 May;25(5):239-44. [Medline: 8835821] [doi: 10.1111/j.1600-0714.1996.tb01378.x]
22. Idris AM, Warnakulasuriya KA, Ibrahim YE, Hartley R, Paterson K, Patel B, Nilsen R, Johnson NW. Characterization of an amorphous deposit in the lamina propria in oral snuff users in the Sudan as collagen. J Oral Pathol Med. 1998 Apr;27(4):157-62. [Medline: 9563570] [doi: 10.1111/j.1600-0714.1998.tb01933.x]
23. Costea DE, Lukandu O, Bui L, Ibrahim MJ, Lygre R, Neppelberg E, Ibrahim SO, Vintermyr OK, Johannessen AC. Adverse effects of Sudanese toombak vs. Swedish snuff on human oral cells. J Oral Pathol Med. 2010 Feb;39(2):128-40. Epub 2009 Oct 4. [Medline: 19804503] [doi: 10.1111/j.1600-0714.2009.00825.x]
24. Loro LL, Vintermyr OK, Ibrahim SO, Idris AM, Johannessen AC. Apoptosis and expression of Bax and Bcl-2 in snuff- and non-snuff associated oral squamous cell carcinomas. Anticancer Res. 2000 Sep-Oct;20(5A):2855-60. [Medline: 11062693]
25. Ibrahim SO, Vasstrand EN, Johannessen AC, Idris AM, Magnusson B, Nilsen R, Lillehaug JR. Mutations of the p53 gene in oral squamous-cell carcinomas from Sudanese dippers of nitrosamine-rich toombak and non-snuff-dippers from the Sudan and Scandinavia. Int J Cancer. 1999 May 17;81(4):527-34. [Medline: 10225439] [doi: 10.1002/(SICI)1097-0215(19990517)81:4<527::AID-IJC4>3.0.CO;2-2]
26. Ahmed HG, Idris AM, Ibrahim SO. Study of oral epithelial atypia among Sudanese tobacco users by exfoliative cytology. Anticancer Res. 2003 Mar-Apr;23(2C):1943-9. [Medline: 12820484]
27. Ahmed HG, Mahgoob RM. Impact of Toombak dipping in the etiology of oral cancer: gender-exclusive hazard in the Sudan. J Cancer Res Ther. 2007 Apr-Jun;3(2):127-30. [Medline: 17998740] [doi: 10.4103/0973-1482.34696]
28. Ahmed HG, Babiker AE. Assessment of cytological atypia, AgNOR and nuclear area in epithelial cells of normal oral mucosa exposed to toombak and smoking. Rare Tumors. 2009 Jul 22;1(1):e18. [Medline: 21139889] [doi: 10.4081/rt.2009.e18] [FREE Full Text]
29. Ahmed HG, Omer AS, Abd Algaffar SA. Cytological study of exfoliative buccal mucosal cells of Qat chewers in Yemen. Diagn Cytopathol. 2011 Nov;39(11):796-800. Epub 2010 Oct 14. [Medline: 20949467] [doi: 10.1002/dc.21462]
30. Edris AM, Ahmed HG, Mohammed EA. Accuracy of oral exfoliative cytology in Sudanese patients undergoing oral biopsy. RSBO. 2011; 8(3):255-60. Available from: http://vdisk.univille.edu.br/community/depto_odontologia/get/ODONTOLOGIA/RSBO/RSBO_v8_n3_julho-setembro2011/RSBO-v8n3-artigo01.pdf
31. Ahmed HG, Diab WMI, Abdulgafar SA, Al-Hazmi AM. Role of quantitative Nuclear Cytomorphometric and NOR dots count in prediction of carcinogenic induced oral cellular proliferative activity. Oncocytology 2011;1:1-6. [doi: 10.5348/ocyj-2011-1-OR-1]
32. Petti S. Lifestyle risk factors for oral cancer. Oral Oncol. 2009 Apr-May;45(4-5):340-50. Epub 2008 Jul 31. Review. [Medline: 18674956] [doi: 10.1016/j.oraloncology.2008.05.018]
33. World Health Organization. Lexicon of alcohol and drug terms. Available from: http://www.who.int/substance_abuse/terminology/who_lexicon/en/. Last access, February 15 2008.
34. Musto DF. The mystery of addiction. Lancet. 1999 Dec;354 Suppl:SIV1. [Medline: 10691419]
35. Rätsch C. The Encyclopedia of Psychoactive Plants: Ethnopharmacology and Its Applications. Rochester, NY: Park Street Press; 2005. p. 564.
36. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang ZF, Berthiller J, Boffetta P. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007 May 16;99(10):777-89. Erratum in: J Natl Cancer Inst. 2008 Feb 6;100(3):225. Fernandez, Leticia [added]. [Medline: 17505073] [doi: 10.1093/jnci/djk179] [FREE Full Text]
37. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer. 2003 Oct;3(10):733-44. Review. Erratum in: Nat Rev Cancer. 2004 Jan;4(1):84. [Medline: 14570033] [doi: 10.1038/nrc1190]

38. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004;83:1-1438. [Medline: 15285078]
39. Idris AM, Ibrahim YE, Warnakulasuriya KA, Cooper DJ, Johnson NW, Nilsen R. Toombak use and cigarette smoking in the Sudan: estimates of prevalence in the Nile state. Prev Med. 1998 Jul-Aug;27(4):597-603. [Medline: 9672954] [doi: 10.1006/pmed.1998.0331]
40. Brunnemann KD, Prokopczyk B, Djordjevic MV, Hoffmann D. Formation and analysis of tobacco-specific N-nitrosamines. Crit Rev Toxicol. 1996;26(2):121-37. Review. [Medline: 8688156] [doi: 10.3109/10408449609017926]
41. Nair J, Ohshima H, Nair UJ, Bartsch H. Endogenous formation of nitrosamines and oxidative DNA-damaging agents in tobacco users. Crit Rev Toxicol. 1996;26(2):149-61. Review. [Medline: 8688158] [doi: 10.3109/10408449609017928]
42. Mosedale JR, Puech JL. Wood maturation of distilled beverages. Food Sci Technol 1998;9(1):95–101. [doi: 10.1016/S0924-2244(98)00024-7]
43. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000 Aug;130(8S Suppl):2073S-85S. Review. [Medline: 10917926] [FREE Full Text]
44. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer. 2007 Aug;7(8):599-612. Review. [Medline: 17646865] [doi: 10.1038/nrc2191]
45. Diet, nutrition and the prevention of chronic diseases. World Health Organ Tech Rep Ser. 2003;916:i-viii, 1-149, backcover. [Medline: 12768890]
46. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of alcoholic beverages. Lancet Oncol. 2007 Apr;8(4):292-3. [Medline: 17431955] [doi: 10.1016/S1470-2045(07)70099-2]
47. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008 Aug;67(3):253-6. Epub 2008 May 1. Review. [Medline: 18452640] [doi: 10.1017/S002966510800712X]
48. Room R, Babor T, Rehm J. Alcohol and public health. Lancet. 2005 Feb 5-11;365(9458):519-30. Review. [Medline: 15705462]
49. Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S. Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. Eur J Cancer Prev. 2007 Jun;16(3):251-6. [Medline: 17415096] [doi: 10.1097/01.cej.0000228402.53106.9e]
50. Jägerstad M, Skog K. Genotoxicity of heat-processed foods. Mutat Res. 2005 Jul 1;574(1-2):156-72. Epub 2005 Apr 1. Review. [Medline: 15914214] [doi: 10.1016/j.mrfmmm.2005.01.030]
51. Ahmed HG, Ebnoof SO, Hussein MO, Gbreel AY. Oral epithelial atypical changes in apparently healthy oral mucosa exposed to smoking, alcohol, peppers and hot meals, using the AgNOR and Papanicolaou staining techniques. Diagn Cytopathol. 2010 Jul;38(7):489-95. [Medline: 19894260] [doi: 10.1002/dc.21224]
52. Turner DO, Williams-Cocks SJ, Bullen R, Catmull J, Falk J, Martin D, Mauer J, Barber AE, Wang RC, Gerstenberger SL, Kingsley K. High-risk human papillomavirus (HPV) screening and detection in healthy patient saliva samples: a pilot study. BMC Oral Health. 2011 Oct 10;11:28. [Medline: 21985030] [doi: 10.1186/1472-6831-11-28] [FREE Full Text]
53. Chang F, Syrjänen S, Kellokoski J, Syrjänen K. Human papillomavirus (HPV) infections and their associations with oral disease. J Oral Pathol Med. 1991 Aug;20(7):305-17. Review. [Medline: 1654422] [doi: 10.1111/j.1600-0714.1991.tb00936.x]
54. Campisi G, Panzarella V, Giuliani M, Lajolo C, Di Fede O, Falaschini S, Di Liberto C, Scully C, Lo Muzio L. Human papillomavirus: its identity and controversial role in oral oncogenesis, premalignant and malignant lesions (review). Int J Oncol. 2007 Apr;30(4):813-23. Review. [Medline: 17332919]
55. Kumaraswamy KL, Vidhya M. Human papilloma virus and oral infections: an update. J Cancer Res Ther. 2011 Apr-Jun;7(2):120-7. Review. [Medline: 21768696] [doi: 10.4103/0973-1482.82915]
56. Eversole LR. Papillary lesions of the oral cavity: relationship to human papillomaviruses. J Calif Dent Assoc. 2000 Dec;28(12):922-7. [Medline: 11323946]
57. Gonzįlez Intxaurraga MA, Stankovic R, Sorli R, Trevisan G. HPV and carcinogenesis. Acta Dermatol 2002;11:3.
58. Ibrahim SO, Warnakulasuriya KA, Idris AM, Hirsch JM, Johnson NW, Johannessen AC. Expression of keratin 13, 14 and 19 in oral hyperplastic and dysplastic lesions from Sudanese and Swedish snuff-dippers: association with human papillomavirus infection. Anticancer Res. 1998 Jan-Feb;18(1B):635-45. [Medline: 9584046]
59. Ahmed HG, Eltoom FM. Detection of Human Papilloma virus Types 16 and 18 among Sudanese patients with oral squamous cell carcinoma. The Open Cancer Journal 2010 (3):1-5. [doi: 10.2174/1874079001003010130]
60. Ahmed HG, Mustafa SA, Eltom FM, Babiker AY. Frequency and genotype of human papillomavirus among Sudanese patients with head and neck tumours. Ecancermedicalscience. 2012;6:282. Epub 2012 Dec 4. [Medline: 23226164] [doi: 10.3332/ecancer.2012.282] [FREE Full Text]
61. Jalouli J, Ibrahim SO, Sapkota D, Jalouli MM, Vasstrand EN, Hirsch JM, Larsson PA. Presence of human papilloma virus, herpes simplex virus and Epstein-Barr virus DNA in oral biopsies from Sudanese patients with regard to toombak use. J Oral Pathol Med. 2010 Sep;39(8):599-604. Epub 2010 Jul 2. [Medline: 20618612] [doi: 10.1111/j.1600-0714.2010.00910.x]

62. Jalouli J, Jalouli MM, Sapkota D, Ibrahim SO, Larsson PA, Sand L. Human papilloma virus, herpes simplex virus and epstein barr virus in oral squamous cell carcinoma from eight different countries. Anticancer Res. 2012 Feb;32(2):571-80. [Medline: 22287747]
63. Dysvik B, Vasstrand EN, Lųvlie R, Elgindi OA, Kross KW, Aarstad HJ, Johannessen AC, Jonassen I, Ibrahim SO. Gene expression profiles of head and neck carcinomas from Sudanese and Norwegian patients reveal common biological pathways regardless of race and lifestyle. Clin Cancer Res. 2006 Feb 15;12(4):1109-20. [Medline: 16489063] [doi: 10.1158/1078-0432.CCR-05-0115] [FREE Full Text]
64. Ibrahim SO, Lillehaug JR, Dolphine O, Johnson NW, Warnakulasuriya KA, Vasstrand EN. Mutations of the cell cycle arrest gene p21WAF1, but not the metastasis-inducing gene S100A4, are frequent in oral squamous cell carcinomas from Sudanese toombak dippers and non-snuff-dippers from the Sudan, Scandinavia, USA and UK. Anticancer Res. 2002 May-Jun;22(3):1445-51. [Medline: 12168821]
65. Lazarus P, Idris AM, Kim J, Calcagnotto A, Hoffmann D. p53 mutations in head and neck squamous cell carcinomas from Sudanese snuff (toombak) users. Cancer Detect Prev. 1996;20(4):270-8. [Medline: 8818386]
66. Sand L, Jalouli MM, Jalouli J, Sapkota D, Ibrahim SO. p53 Codon 72 polymorphism in oral exfoliated cells in a Sudanese population. In Vivo. 2012 Jan-Feb;26(1):59-62. [Medline: 22210716]
67. Jalouli MM, Jalouli J, Sapkota D, Ibrahim SO, Sand L, Hirsch JM. Differential expression of apoptosis, cell cycle regulation and intermediate filament genes in oral squamous cell carcinomas associated with toombak use in Sudan. Anticancer Res. 2011 Oct;31(10):3345-51. [Medline: 21965745]
68. Mayne ST, Morse DE, Winn DM. Cancers of the oral cavity and pharynx. In: Schottenfeld D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006. p. 674-96. [doi: 10.1093/acprof:oso/9780195149616.003.0035]
69. Suliman NM, Astrųm AN, Ali RW, Salman H, Johannessen AC. Oral mucosal lesions in skin diseased patients attending a dermatologic clinic: a cross-sectional study in Sudan. BMC Oral Health. 2011 Sep 19;11:24. [Medline: 21929814] [doi: 10.1186/1472-6831-11-24] [FREE Full Text]
70. Lucenteforte E, Garavello W, Bosetti C, La Vecchia C. Dietary factors and oral and pharyngeal cancer risk. Oral Oncol. 2009 Jun;45(6):461-7. Epub 2008 Nov 5. Review. [Medline: 18990606] [doi: 10.1016/j.oraloncology.2008.09.002]
71. La Vecchia C, Tavani A. Fruit and vegetables, and human cancer. Eur J Cancer Prev. 1998 Feb;7(1):3-8. Review. [Medline: 9511846]
72. Augustin LS, Gallus S, Franceschi S, Negri E, Jenkins DJ, Kendall CW, Dal Maso L, Talamini R, La Vecchia C. Glycemic index and load and risk of upper aero-digestive tract neoplasms (Italy). Cancer Causes Control. 2003 Sep;14(7):657-62. [Medline: 14575363] [doi: 10.1023/A:1025676907942]

To cite this article:
Ahmed GH. Aetiology of Oral Cancer in the Sudan.
J Oral Maxillofac Res 2013;4(2):e3
URL: http://www.ejomr.org/JOMR/archives/2013/2/e3/v4n2e3ht.pdf
doi: 10.5037/jomr.2013.4203