Review Article

Review of the Literature on Oral Cancer: Epidemiology, Management and Evidence-based Traditional Medicine Treatment

Abstract

Oral cavity cancers are part of the upper aerodigestive tract cancers and represent a significant burden worldwide. Its epidemiology varies from country to country with high frequencies in South East Asian countries. Tobacco and alcohol are the main risk factors. Survival of oral cancer is low i.e., less than 40% in the advanced stage (stage III and IV), diagnosis of oral cavity cancer is based on a complete clinical examination of the oral cavity complete with biopsy, bio-markers are an adjunct to screening and diagnosis of oral cavity cancers, surgery, radiotherapy, chemotherapy and immunotherapy are part of the therapeutic armamentarium of oral cancer but also have limitations. Traditional medicine is an important and proven alternative in the treatment and support of patients with oral cavity cancer. Prevention of oral cavity cancers includes not only early detection of precancerous and cancerous lesions but also control of risk factors and education of the population. Surgery, radiotherapy, chemotherapy and immunotherapy are part of the therapeutic strategy of oral cancer treatment but also have limitations. Traditional Medicine is an important and proven alternative in the treatment and support of patients with oral cavity cancer. It is thus desirable to scientifically validate phytochemicals in order to integrate alternative medicine as part of national cancer management strategy. *In silico* advanced studies on secondary metabolites of medicinal plants traditionally used to treat oral cancer are in progress.

Keywords: Oral cavity cancer, Upper Aerodigestive Tract, Evidence-based Medicine, Phytochemicals, Medicinal plants, Alternative/Traditional Medicine

1. Introduction

Cancers of the oral cavity (COC) are part of the cancers of the upper aerodigestive tract (UADT) and share the same epidemiological characteristics [1, 2]. Cancer of the UADT is the sixth most common clinical form of cancer in the world [3, 4, 5]. Between 30 and 40% of VADS cancers are oral cavity cancers (OCCs) [6, 7]. It often presents as an ulcerated lesion with an indurated base [8, 9]. Squamous cell carcinoma is the most common histological subtype and accounts for over 90% of OCCs [6, 7, 10]. Other types of cancers (salivary gland cancers, sarcomas, lymphomas, melanomas) account for less than 10% of OCCs, and about 1% are metastatic cancers of the lung, breast, prostate, and kidney [11,12].

The development of OCC depends on epigenetic and genetic factors. This tumor process takes place in several stages, starting with some changes in the oral mucosa, followed by the development of invasive cancer until the appearance of metastases [13]. The aim of this literature review is to discuss the epidemiology of OCC, some risk factors, and means of diagnosis and treatment as well as

prevention of OCC. The articles selected for this literature review were in English and French after selection on Google scholar and PubMed search engines from 2010 to 2021. All articles related to OCCs dealing with epidemiology, risk factors, treatment, and prevention were included in this literature review.

2. Literature

2.1. Epidemiology

OCC accounts for 2% of all cancers, with an estimated 377,713 new cases in 2020 and 177,384 deaths worldwide [5,14]. The actual epidemiological data on OCC are not homogeneous.

They vary from one country to another, with high frequencies in South East Asian countries [5,14]. In developed countries, 75% of oral cancers are related to tobacco and alcohol consumption [3]. In contrast, in low-income countries, the high incidence of OCCs is due not only to tobacco and alcohol consumption, but also to betel nut consumption, especially in Southeast Asia [15 ,16], and nitrosamine-rich foods such as smoked and salted fish, infections, poor nutrition, and exposure to carcinogenic foods [3].

India, Pakistan, Bangladesh, and Sri Lanka have some of the highest numbers of diagnosed OCC in the world [17-19]. In Pakistan, OCC accounts for nearly 19.2% of all diagnosed cancers [20]. In India, it accounts for 30-50% of all cancers and is a major public health problem [19, 21]. In the Middle East, 8,928 cases of OCC are reported each year, representing 1.5% of all cancers, with a case fatality rate of 1% (3,573 cases) [22]. France is among the most affected countries in Europe with almost 12,080 new cases in 2017, 68% in men and 32% in women [23]. In the US, OCC accounted for nearly 2.9% of all diagnosed cancers and 1.6% of deaths in 2018 [24].

In Africa, data is scarce due to the lack of cancer registries in many countries. However, the few studies carried out across Africa have given an idea of the frequency of the disease. In Kenya, Onyango et al. [25] found in their study the frequency of OCC to be between 2 and 3.6% of UADT cancers. In the Democratic Republic of Congo (DRC), studies of OCC have reported a frequency of between 1.8% and 2.3% [26, 27].

2.2. Risk factors

OCC is a multifactorial disease [8], depending on a number of factors that may be unique to the individual and/or related to the environment, genetics, and local and infectious factors. Carcinogenesis takes place in three stages: initiation by which an irreversible lesion is transmitted to so-called initiated daughter cells; promotion during which the initiated cells proliferate and constitute a clone at the origin of the cancer; and finally the progression characterized by local and lymphatic invasion and by metastases. The development of UADT is the consequence of a multi-step process with progressive molecular and genetic changes that ultimately results in the transformation of normal mucosa into invasive cancer. More than 50% of pre-malignant lesions carry a mutation of the P53 tumor suppressor gene. Head and neck cancers express 80–90% of their total epidermal growth factor receptor (EGF-R) repertoire [8, 28, 29].

2.2.1. Potential malignant lesions

Potentially malignant oral epithelial lesions or disorders include both clinical lesions and oral dysplasia, which should be reserved specifically for lesions with histopathological proven foci of dysplasia [30]. According to the most recent World Health Organization recommendations [31, 32], they have a statistically increased risk of progressing to cancer and are sufficient to cover pre-cancerous lesions and pre-cancerous conditions.

70% of OCCs are preceded by a potentially malignant lesion [6]. Pre-cancerous lesions of the oral cavity mainly include leukoplakia, erythroplakia, submucosal fibrosis, lichen planus, lupus erythematosus, and actinic cheilitis [31-34]. Tobacco and alcohol are the most common risk factors for precancerous lesions of the oral cavity [30, 34]. The treatment for these lesions consists of removing the risk factors and monitoring the lesions on a regular basis for early detection of possible transformation into cancer cells [32, 33]. However, Ganesh et al. reported that surgery on these lesions does not reduce the rate of transformation of these lesions into oral cancer [35].

2.2.2. Tobacco and alcohol

Tobacco use is the leading cause of death in the world, accounting for over 7 million deaths each year, or 44% of all deaths from non-communicable diseases [36]. All forms of tobacco are carcinogenic [37]. 80 to 90% of OCC patients are smokers and the risk increases with the amount of tobacco smoked and its duration [2, 38 – 40]. The use of one pack of tobacco per day for 20 years or two packs per day favors the development of oral cancer [39, 41]. This can be explained by the fact that tobacco contains several chemical substances, in particular nicotine, which diffuses rapidly into the brain and leads to a strong dependency [2, 42]. In addition, tobacco contains polycyclic hydrocarbons and nitrosamines, which are carcinogenic and irritants that interfere with host DNA (desoxyribonucleic acid) and eventually lead to oral cancer [42-45].

Alcohol is classified as a carcinogen by the International Agency for Research on Cancer (IARC) [46]. 75% of people with bluetongue consume alcohol [40]. According to the WHO, more than 3 million people died from alcohol abuse in 2016, i.e., one in twenty deaths worldwide is due to alcohol [47]. Alcohol consumption is a significant risk factor for some chronic non communicable diseases, including cardiovascular disease, diabetes, and certain cancers [47, 48]. It is involved in DNA hypo-methylation. This leads to loss of control of proto-oncogene expression, increased mucosal permeability, liver damage, and decreased immunity and salivary flow [13, 38, 39, 41]. Alcohol and tobacco have a synergistic effect on the occurrence of oral cancers [39-43]. Unfortunately, alcohol and tobacco consumption are increasing rapidly in Africa [49].

2.2.3. Oral hygiene

Poor oral health and hygiene are frequently associated with OCC [50, 51]. Poor oral hygiene promotes the development of oral cancers by increasing the oral flora with bacteria that will increase the amount of acetaldehyde following the breakdown of ingested alcohol [51-54].

2.2.4. Viruses

There are over 200 HPV (human papilloma virus) stereotypes, six of which are implicated in cancer, including HPV16 and 18 [53, 54] and are more commonly found in normal tissues [54, 55]. HPV16 and 18 express the E6 and E7 oncoproteins which inhibit tumor suppressor proteins encoded by the

P53 and Rb genes respectively, leading to disruption of cell regulation [4, 32, 56]. Multiple sexual partners and oral sex with more than six partners may contribute to the development of OCC due to HPV [57]. The carcinogenic role of the HIV (Human immunodeficiency virus)/AIDS (Acquired immunodeficiency syndrome) has also been suggested by a decrease in the immunity of affected individuals, leading to the development of certain HIV-associated tumors in the oral cavity such as lymphomas and Kaposi's sarcoma [57-59]. Epstein-Barr virus (EBV) disrupts host DNA and can result in oral leukoplakia and adenocarcinomas [31, 51].

2.2.5. Trauma

Chronic trauma to the oral mucosa is the repetitive result of mechanical action caused by injury from an irritant [60]. This irritating agent can be a defective tooth (fractured, badly positioned); a bad dental filling [13, 60]. Chronic trauma, especially from ill-fitting dentures in the mouth, can be an activator of the carcinogenic process, especially if other risk factors are added [1, 29, 61]. These chronic microtraumas modify the mucous membrane, leading to keratinization.

2.2.6. Nutritional factors

A diet rich in vegetables and fruit is linked to a reduced risk of oral cancers because fruits and vegetables contain vitamins, particularly A, C, D, and E, which are antioxidants that reduce the risk of cancers of the upper aerodigestive tract [59, 62, 63]. However, a diet rich in meat, salted and smoked fish increases the risk of developing OCCs due to the presence of nitrosamines, which are carcinogenic [3].

2.2.7. Genetic predispositions

Not everyone who is exposed to carcinogenic factors can develop cancer; only a proportion develops it as a result of factors intrinsic to the individual [29, 43]. The deleterious effect of a particular carcinogen varies from one person to another and from one region to another [29]. The P53 protein is a tumor suppressor gene that prevents carcinogenesis by triggering cell cycle arrest, and 40-70% of OCCs have mutations in the P53 gene, leading to the formation of a non-functional product [64]. 90% of these mutations are located between exons 5 and 8 of TP53, which is a region where most mutations occur, including R175, G245, R248, R249, R273 and R282 in the DNA binding domain [65, 66]. Thus, people with syndromes caused by the mutation of certain genes have an increased risk of developing OCC, as in Fanconi anaemia, where this risk is 100 times higher than in the normal population [67, 68].

2.2.8. Gender and age

OCCs are more common in men than in women [69-71]. The use of alcohol and tobacco is thought to be at the root of this male predominance of OCCs. Although a female ascendancy has been noted following an increase in tobacco and alcohol consumption in women [29, 72], according to a study by Luo et al. [73], the high levels of hormones, particularly oestrogens, in women play a protective role against OCC compared with men. A median age of around 50 has been found in the majority of studies [74-76].

However, due to the increased use of tobacco and alcohol among young people, several cases of cancer have been observed before the age of 50 [77]. HPV infection and genetic predisposition are

thought to be the basis of this infection in young people, as well as risky sexual behaviour such as oral sex [77, 78].

2.2.9. Exposure to the sun's UV rays

Exposure to UV (ultraviolet) radiation from the sun is a risk factor for lip cancer. The lower lip is the most exposed to this disease [79, 80]. The people most affected by this cancer are outdoor workers such as farmers, fishermen, masons, etc. [80, 81]. This lesion often appears between the fifth and seventh decades as a result of accumulated exposure to UV radiation from the sun [80, 82].

2.3. Other factors

Marijuana use, betel nut addition, people with low social status, mouthwash containing alcohol, chronic candidiasis, and aging [13,15-17, 24, 29-35].

2.4. Location

The tongue is the site most affected by OCC [83, 84, 85]. This can be explained by the central position of this organ in the oral cavity. It is constantly exposed to carcinogenic substances such as tobacco and alcohol [85, 86] and plays an important role in mastication, phonation, and swallowing [85]. Cancer of the tongue occurs most frequently in men aged 60-70 years [85-87]. Other common sites of OCC are the lips due to sun exposure and smoking, the gums, the floor of the mouth; and the inner cheeks due to certain habits such as alcohol and chewing tobacco consumption [88-89].

2.5. Inflammation and oral cancer

Inflammation is the main feature of cancer [90]. About 15% of cancers are due to inflammatory processes [91]. Chronic inflammation plays an important role in the development of VADS cancers [90-94]. Several inflammatory mediators are involved in OCC carcinogenesis, including nuclear factor kappa B (NK-KB), vascular endothelial growth factor (VEGF), p53, nitric oxide (NO), reactive oxygen species (ROS), nitrogen species, specific micro RNAs (miRNAs), cytokines [tumor necrosis factor alpha (TNF-α), interleukins (IL-1, IL-6, IL-8)], prostaglandins, and COX-2 (cyclooxygenase 2) [91-97]. The expression of these mediators is largely responsible for a pro or anti-tumorigenic inflammatory response through changes in cell proliferation, cell death, cell senescence, DNA mutation, and DNA methylation [91, 95]. These inflammatory mediators are involved in angiogenesis, tumor growth, and the proliferation of tumor metastases [91-100]. NO (Nitric oxide) plays an active role in free radical and tumor biology [101]. Overexpression of COX-2 is found in 80% of potentially malignant lesions and cancers of the UADT and this overexpression is associated with lymphatic metastasis [97-100].

2.6. Biopsia

Several tests are used for the diagnosis of OCC, such as oral cytology, toluidine blue test, oral cytobrush, and light-based tests [102-105]. Clinical examination of the oral cavity supplemented by biopsy followed by histopathological examination remains the diagnostic reference examination, as other techniques have limitations such as false positives, lack of structural analysis, superficial samples [103-106].

The only examination that accurately determines the exact limit, benignity or malignancy of a lesion, its dysplastic character, and the in situ or invasive evolution of a cancerous lesion is a biopsy [102,107].

2.7. Biomarkers

Biomarkers are normal biological indicators of pathogenic processes or responses to exposure or intervention [108]. The use of biomarkers from biological fluids (blood, urine, saliva) facilitates the early diagnosis of cancers [109]. Saliva contains factors such as cytokines, DNA and RNA (ribonucleic acid) molecules, circulating cells, tissue derivatives, and extracellular vesicles that can be used as biomarkers in OCCs [110]. Salivary biomarkers are proposed as important adjuncts in the diagnosis and screening of OCCs and potentially malignant lesions [111]. More than 100 salivary molecules have been identified as potential biomarkers of OCCs [112]. IL1ß, IL6 and IL8 are useful for the early detection and screening of OCCs and potentially malignant injuries (PMIs) [113], as they are involved in the pathogenesis of OCCs and the transformation of PMIs [113-114]. Currently, genomic techniques (like high-throughput sequencing) and artificial intelligence are being exploited in the search for molecular/circulating tumor biomarkers. These new tools facilitate early detection and personalized therapeutic management. The detection of circulating tumor cells and/or circulating tumor DNA in blood samples, a process called "liquid biopsies", provides a genetic profile of the patient's tumor. This method of molecular characterization and real-time monitoring of the disease facilitates the search for possible relapses, the emergence of resistance or a new therapeutic target. In the long term, these liquid biopsies could thus provide a means of early detection of cancer that does not require a biopsy of the tumor tissue itself [115].

2.8. Oral cancer treatment

Several treatment protocols for oral cancer exist and depend on the nature of the cancer, the age of the patient, and the TNM (Tumor node metastasis) stage [116-118]. The treatment plan for OCC is decided in a collegial manner in an interdisciplinary meeting after clinical, radiological, and endoscopic assessment [102, 114]. Surgery remains the main treatment for OCC but is associated with massive disfigurement, inability to perform normal oral functions, psychosocial stress, and extensive rehabilitation [10, 117-119].

Radiotherapy, chemotherapy, or immunotherapy is also part of the therapeutic armamentarium, and palliative treatment is indicated for non-operable cases [10, 116, 119]. Radiotherapy and chemotherapy also have limitations in terms of significant toxicities or resistance to treatment, all of which compromise patients' quality of life and well-being [117-119]. In addition, recurrence and/or metastasis are found in more than half of patients after several years of primary cancer treatment (80% of the cases occur after the first two years), leading to recurrent cancer growth [116-120].

2.9. Evidence-based Traditional Medicine in the treatment of oral cancer

More than 80% of the world's population uses traditional medicine for cultural, economic, or accessibility reasons [121]. Several studies worldwide have confirmed the importance of this medicine in the treatment of cancers in general and those of the oral cavity in particular [122-124]. It is currently recognized that modern cancer therapies have demonstrated their limitations in terms of their inability to completely eliminate tumor cells, drug resistance, and other adverse effects [122,123]. Given these drawbacks, there is a growing interest in traditional medicine, particularly herbal medicine, which is used by 80% of the population in developing countries for the treatment of various diseases, including cancer [122-124]. There is evidence that this medicine improves the effectiveness of chemotherapy,

radiotherapy, targeted therapy, and immunotherapy [123]. It is believed to act on cancer by inhibiting tumor progression and improving the immune system [123]. Medicinal plants have been widely used as a natural source of remedies to cure multiple diseases, including cancer [125]. Among the most widely used herbs are: green tea extract, which contains large amounts of polyphenols including epigallocatechin 3-gallate (EGCG), has anti-cancer and anti-inflammatory properties and induces cell cycle arrest and apoptosis by activating p53 and targeting p21 and Bax [126, 127].

Ginger contains gingerol, paradol, and zingerone, and has antioxidant, anti-inflammatory, anti-ulcerogenic, and anti-carcinogenic properties [128]. Turmeric is a spice derived from turmeric (*Curcuma longa*), has anti-carcinogenic properties in UADT cancers as a result of its anti-inflammatory effects in decreasing NF-KB and pro-apoptotic regulation. Turmeric has a phagocytic action on free radicals, inhibits lipid peroxidation and decreases tumor cell proliferation by suppressing angionesis and reducing tumor growth and metastasis by activating p53 and p21 [13, 128, 129]. According to the study by Wang et al., coffee consumption reduces the risk of oral cavity cancer [130]. Garlic, honey, polyphenols, flavoids, anthocyanins, saffron, lycopene, and raspberry also have anti-cancer properties against OCC [13, 128, 129, 131].

2.10. Survival and prevention

The five-year survival rate of OCC has not improved despite progress in treatment; it is about 40% when diagnosed at advanced stages III and IV and 80% when diagnosed at early stages I and II [132, 133]. The prevention of oral cancer is multisectoral at the level of government, civil society, and oral practitioners. The fight against social inequalities and awareness campaigns against the production, advertising, and consumption of tobacco and alcohol [136].

Educate the population to have a healthy lifestyle, good oral health, and good sexual health [136]. OCC screening therefore constitutes an essential component of the routine head and neck examination performed in primary dental care practices [6].

3. Conclusion and suggestions

This review of the literature has shown the different facets of OCC in terms of both epidemiology and management. OCC is a multifactorial disease involving several endogenous and exogenous risk factors. Knowledge of the epidemiology, the different risk factors, the crucial role of inflammation and genetics in the development of OCC, as well as the different diagnostic and treatment techniques, is necessary for the screening and management of cancer patients.

Surgery, radiotherapy, chemotherapy, and immunotherapy are part of the therapeutic strategy of oral cancer treatment but also have limitations. Traditional medicine is an important and proven alternative in the treatment and support of patients with oral cavity cancer. It is thus desirable to scientifically validate phytochemicals in order to integrate alternative medicine as part of the national cancer management strategy. *In silico* advanced studies on secondary metabolites of medicinal plants traditionally used to treat oral cancer are in progress.

In memoriam

We are indebted to you, Professor Pakasa Muyulu Nestor, for initiating the present research project. Here are today's fruits of your effort, which you do not consume. We will keep your wise counsel and

good manners. May your soul rest in peace and may the land of our ancestors be sweet and light to you.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References

1. Bugsham A, Farooq I. Oral squamous cell carcinoma: metastasis potentially associated malignant disorders, etiology and recent advancements in diagnosis. F1000 Research. 2020: 9.
2. Jiang X, Wu J, Wang J, Huang R. Tobacco and oral squamous cell carcinoma: A review of carcinogenic pathways. Tob Induc Dis. 2019; 17:29.
3. Omitola OG, Soyele OO, Sigbeku O, Okoti O et al. A multi-Centre evaluation of oral cancer in Southern and Western Nigeria: An African oral pathology research consortium initiative. Pan African Medical Journal 2017; 28: 64.
4. Gupta S, Gupta S. Role of human papillomavirus in Oral Squamous cell carcinoma and oral potentially malignant disorders. A review of the literature. Indian J Dent 2015; 6: 91-8.
5. Bray F, Ferlay J, Soerjormataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424.
6. FDI 2018, Le Cancer Buccal prévention et prise en charge. https://www.fdi.worlddental.org.
7. Badri P, Ganatra S, Baracos V, Lai H, Amin M. Oral Cavity and Oropharyngeal Cancer Surveillance and Control in Alberta; A Scooping Review.J Can Dent Assoc 2021; 87 :14.
8. Nalin AS, Mary J, Leukose T, Sreedhar S, Padiath S. Traumatic ulcer-miming squamous cell carcinoma J. of Dental and Medical Science 2016; 15(3) :83-86.
9. Bauckaert M, Munzhelele TT, Feller L, Lemmar J and Khamissa RAG. The clinical characteristics attending the Medunsa oral health Centre, South Africa. Integr Cancer Sci. Therap 2016; 3(5): 575-78.
10. Paré A, & Joly A. Cancers de la cavité buccale : Facteurs de risque et prise en charge. J. LPM 2017; 46(3):320-30. Paré A, et Joly A. Cancers de la cavité buccale: Facteurs de risque et prise en charge. J. LPM 2017; 46(3): 320-30.
11. Wong T, Wiesenfeld D. Oral Cancer. Australia Dental Journal. 2018; 63: S91-S9.
12. Parvin Yavari. Epidemiology textbook of prevalent diseases in Iran (cancers). First edition. Volume 3. Teheran. 2014
13. Irani S. New Insights into oral cancer-Risk Factors and prevention: A Review of Literature. Int J Prev Med 2020; 11: 202.
14. Globocan, 2020 : Lip, Oral Cavity. htpps://www.iarc. Consulté le 03 /04/2022
15. Siddiqi K, Scammell K, Huque R, Khan A, Baral S, Ali QS et al. Smokeless Tobacco supply chain in South Asia: A comparative analysis using the WHO. Framework Convention on Tobacco control, Nicotine Tob Res 2015; 18: 424-30.
16. Pahwa V, Nair S, Shetty RS, Kamath A. Prevalence of oral Premalignant Lesions and its Risk Factors among the Adult population in udupi Taluk of Coastal Karnataka, India. Asian Pac J Cancer Prev 2018; 19 (8): 2165-2170.
17. Sharma P, Saxena S, Aggarwal P. Trends in the epidemiology of oral squamous cell carcinoma in Western UP: an institutional study. Indian J Dent Res. 2010; 21(3): 316-319.

18. Zhang SZ, Xie L, and Shang ZJ. Burden of Oral Cancer on the 10 most populous countries from 1990 to 2019.Estimates from the global burden of Diseases study. Int. Environ Res Public Health 2022; 19: 875.
19. Tandon A, Bordoloi B, Jaiswa R, Srivastava A, Singh B, Shafique U. Demographic and clinicopathological profile of oral squamous cell carcinoma patients of North India: A retrospective institutional study. SRM J Res Dent Sci 2018; 9:114-8.
20. Qureshi MA, Syed SA, Sharafat S. Lip and oral cavity cancers (C00-C06) from a mega city of Pakistan: Ten –year data from the Dow Cancer Registry. J Taibah Univ Med Sc 2021; 16(4): 624-627.
21. Kokila S, Prassad H, Rajmohan M, Srichintu KR, Mahalakshmi L, Shanmuganathan S, Prema E. Evaluation of Micronuclei and Cytomorphometric changes in patients with Differents Tobacco Related Habits using Exfoliated Buccals Cells. Asian Pac J Cancer Prev 2021; 22 (6):1851.
22. Kujan.O, Farah.C & Johnson.N. Oral and Oropharyngeal Cancer in the Middle East and North Africa: Incidence, mortality, trends and gaps in the public databases a presented to the global and cancer forum. Translational Research in Oral Oncology 2017; 2(1):1-9.
23. https://www.cancer.ca/fr.ca/cancer/information/cancer-type/oral (07 Mars 2018).
24. American Dental Association (ADA). Oral Cancer, 2018.
25. Onyango JF, Omondi BI, Nyiru A, Awange OO. Oral cancer at the Yata National Hospital, Nairobi. East African Medical Journal 2004; 1816: 318-321.
26. Mashinda K.A, Kayembe KP, Mapatano MA ; Prévalence du cancer en RDC : données anatomopathologiques recueillis aux CUK à l'HGRK. Ann.Afr.Med. 2012; 5(3) :1087-1093.
27. Mfutu C, Pakassa NM, Sekele JPI, Nzudjom AF, Bolenge JI, Nyembwe DC, Ngbolua KN. Evaluation of oral cavity cancers frequency in patients attending dentistry and maxillofacial surgery service of Kinshasa university hospital (Democratic Republic of the Congo): A cross-sectional study. IJADS 2019; 5(4): 293-296.
28. ARC (cancer): le diagnostic. Fondation ARC pour la recherché sur le cancer. htpps://www.fondation.arc.org. (23/4/2021).
29. Gauzeran D. Lésions à risque aux cancers des muqueuses orales. 2éd. Courbevoie: Editions Cdp, 2014; pp. 62-112.
30. Awadallah M, Idle M, Patel K, Kademani D, Management update of potentially premalignant oral epithelial lesions. Oral Surg Oral Med Oral Pathol Oral Radiol 2018; 125(6): 628-636.
31. Warnakulasuriya S. Clinical features and features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018; 125(6): 582-590.
32. Speight PM, Khuram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018; 125(6): 612-627.
33. Mustafa E, Parmar S, Praveen P. Premalignant lesions and conditions of the Oral Cavity. In: Bonanthaya K, Panneerselvam E, Manuel S, Kumar V.V, Rai A.(eds) Oral and Maxillofacial Surgery for the clinician. Springer, Singapore. httpps://dpi.org/10.1007/978-981-15-1346-6_80.
34. Ganesh D, Sreenivasan P, Ohman J, Wallstrom M et al. Potentially Malignant Oral disorders and cancer transformation. Anticancer Research 2018; 38: 3223-29.
35. Sathiasekar AC, Mathew DG, JaishLal MS, Arul Prakash AA, Goma Kumar KU. Oral field cancerization and its clinical implications in the management in potentially malignantdisorders.J.Pharm. Bioallied Sci 2017; 9(suppl 1): S23-5.
36. OMS, Journée mondiale sans tabac 2018 tabac et cardiopathies. https : //www.who.int.2018.event (13 janvier 2019).
37. Département Prévention Cancer Environnement. https://www.cancer-environnement.fr. (13/08/2021).
38. Radoi LS, Paget- Bailly F, Guida D, Cyr G, Menvielle A, Schmaus M, Carton et al. ¨Family history of cancer, personal history of medical conditions and risk of oral cavity cancer in France: the ICARE study. BMC Cancer 2013; 1:1-23.

39. Lee YCA, Li S, Li Q, Chen CJ, HSU WL, et al. Tobacco Smoking, alcohol drinking, betel quid chewing and the risk of Head and Neck Cancers in East Asian population. Head Neck 2019; 41(1): 92-102.
40. Facteurs de risque de cancer de la cavité buccale htpps://www.cancer-environnement.fr. (13/08/2021).
41. Tenore G, Nuvoli A, Mohsen A, Cassoni A et al. Tobacco, Alcohol and Family History of Cancer as Risk Factors of Oral Squamous Cell Carcinoma: Case-Control Retrospective Study. Appl. Sci. 2020; 10: 3896.
42. Sanner T and Grimsrud TK. Nicotine carcinogenicity and effects on response to cancer treatment-a review. Front. Oncol. 2015; 5:196.
43. Ali J, Sabitha B, Jan HIJ, Haider SA, Khan AA, Ali SS. Genetic etiology of oral cancer. Oral Oncology 2017; 70: 23-28.
44. Binmadi N, Harere L, Mattar A, Aljohani S, Alhindi N,Ali S, Almazrooa S.Oral lesions Associated with smokeless users inSaudiArabia:Single center cross-sectional study. Saudi Dental Journal 2020; 34:114.
45. Monika S, Dineshkumar T, Priyadharini S, Niveditha T,SK P, Rajkumar K.. Smokeless tobacco products (STPs) harbor bacterial populations with potential for oral carcinogenicity. Asian Pac. J. Cancer Prev. 2020; 21: 815-824.
46. IARC: Monographs on the evaluation of carcinogenic risks to human's volume 100E.personal habits and indoor combustion. htpps://publications.iarc.fr/book and Report. Series/iarc-Monographs-on-the-identification-of Cacinogenic-hazars-To-Humans/Personal-Habits–and–indoor-combustions-2012.
47. World Health Organization Global status Report on Alcohol and health 2018, World Health Organization: Geneva, Switzerland, 2018.
48. Rehm J, Gmel Sr, Gmel G et al. The relationship between different dimensions of alcohol use and the burden of disease –an update. Addiction 2017; 112: 968-1001.
49. Aliam, les Cancers en Afrique Francophone, www.att.aliam.org. (25/11/2018).
50. Chang JS, Lo HI, Wong T-Y, Huang C-C, et al. Investing the association between oral hygiene and head and neck cancer. Oral Oncol. 2013; 49(10).
51. Mathur R, Singhavi HR, Malik A, Nair S, Chaturvedi P. Role of poor oral hygiene in causation of oral cancer.A Review of Literature.Indian J Surg Oncol 2019; 10(1): 184-195.
52. Huang J, He B, Chen F Liu F, Yan L, Hu Z, Lin L, He F, Cai L. Association between oral hygiene, chronic diseases and oral squamous cell carcinoma. Zhonghua Yu Fang Yi Xue Za Zhi, 2015; 49: 688.
53. Rupe C, Basco A, Schiavelli A, Cassano A, Micciche F, Galli J, Cordaro M, Lajolo C. Oral Health status in patients with head and Neck Cancer before Radiotherapy: baseline Description of an observational prospective study. Cancers 2022; 14:1411.
54. Melo BA, Vilar LG, Oliveira NR, Lima PO, Pinheiro MB ,Domingueti CP, Pereira MC. Human papillomavirus infection and oral squamous cell carcinoma: A systematic review. JORL 2021; 87(3): 346-352.
55. Kim SM. Human papillomavirus infection and oral squamous cell carcinoma-a systematic review.JORL.2021; 87(3): 346-352.
56. Tulay P, Serakinci N. The role of human papilloma viruses in cancer progression. Cancer Metastasis Trent 2016; 2: 201-213.
57. Gené D. Fellation non protégé: quel risqué? Rev Med Suisse 2013; 9:1828-31.
58. Chen CH, Chung CY, Wang LH, Lin C, Lin HL, Lin HC. Risk of cancer among HIV-infected patients from a population-based nested case-control study: implications for cancer prevention. BMC Cancer 2015; 15:133.
59. Speicher DJ, Ramirez-Amador V, Dittmer DP, Cyriaque JW, Goodman MT, Moscicki AB. Viral infections associated with oral cancers and diseases in the context of HIV: Workshop 3B. Oral Dis. 2016; 22(Suppl1):181-192.

60. Nagarajappa AK, Trauma induced Oral Malignant ulcer: A case report. Harmoniz. Res. Med. and Hlth. Sci. 2015; 2(4): 206-209.
61. Thongprasom K, Phattarataratip E. Chronic Oral Mucosal Trauma and oral cancer: A series of cases. Arch. Dent 2019; 1(1):16-20.
62. Rodriguez- Molinero J, Migueláñez- Medrán BdC, Delgado-Somolinos E, Martin Carreras-Presas C, Fernández-Farhall J, López-Sánchez AF. Association between Oral Cancer and Diet: An Update. Nutrients 2021; 13: 1299.
63. Lauriitano D, Lucchese A, Contaldo M, et al. Oral squamous cell carcinoma diagnostic markers and prognostic indicators. J Biol Regul Homeost Agents 2016; 30:169.
64. Usman S, Jamal A, Waseem A. Major Molecular signaling pathways in Oral Cancer associated with therapeutic Resistance. Front Oral Health 2021; 1: 630160
65. Heent Z,Mohr A, Bhakta-Guha D. Efferth T. The role of P53 in cancer drug resistance and target chemotherapy. Oncotarget 2017; 8: 8921-46.
66. Rogha M, Berjis N, Lajevardis M, Alandaran M, Hashemi SM. Identification of R29 mutation in P53 gene in tumoral tissue of tongue cancer. Int J Prev Med 2019; 10:129. doi: 104103ijpm.IJPVM.5017.
67. Furquim CP, Pivovar A, Amenabor JM,Bonfin C, Torres- Pereira CC.Oral Cancer in Fanconi Anemia. Review of 121 cases. Crit Rev Oncol Hematol 2018; 125: 35-40. doi: 10.1016/j.critrevonc.2018.02.013.
68. Alter BP.Cancer in Fanconi anemia 1927-2001.Cancer 2003; 97: 425-440.
69. Muange P, Chindia M, Njiru W, Dimba E. Oral squamous cell carcinoma :A 6-Month Clinico-Histopathologic Audit in a Kenyan Population. Open journal of stomatology 2014; 04(10): 475-483.
70. Brito RT, Perazzo MF, Peixoto TS, et al. The clinical staying of oral squamous cell carcinoma. Rev. Salud. Publica 2018; 20(2): 221-25.
71. Lee YCA, Li S, Li Q, Chen CJ, HSU WL, et al. Tobacco Smoking, alcohol drinking, betel quid chewing and the risk of Head and Neck Cancers in East Asian population. Head Neck 2019; 41(1) 92-102.
72. Lee YC, Young CK, Chien HT, Chin S, et al. Characteristics and outcomes differences in male and female oral cavity patients in Taiwan. Medicine 2021; 100(44): e26747.
73. Luo SD, Chiu TJ, Chen WC and Wong LS. Sex differences in otolaryngology: focus on the Emerging Role of oestrogens in inflammatory and pro- Resolving Responses. Int. J. Mol. Sci 2021; 22: 8768.
74. Dhanutai K, Rojanawatsirivej S, Thosaporn W, Kinterak S, et al. Oral Cancer: A multicenter Study Med Oral Patol Oral Cir Bucal 2018; 23(1): e23-9.
75. Siddiqi K, Scammell K, Huque R, Khan A, Baral S, Ali QS et al. Smokeless Tobacco supply chain in South Asia : A comparative analysis using the WHO .Framework Convention on Tobacco control, Nicotine Tob Res 2015; 18: 424-30.
76. Bai XX, Zhang J and Wei L. Analysis of primary oral and oropharyngeal squamous cell carcinoma in inhabitants of Beijing China-a 10 –year continuous single-center study. BMC Oral Health 2020; 20: 208.
77. Paderno. A, Morello.R, Piazza.C. Tongue carcinoma in young adults: a review of the literature. Acta Otorhinolaryngologica Italica 2018; 38:175-180.
78. Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA. Increase in head and neck cancer in younger patients due to human papillomavirus (HPV).oral Oncol. 51(8): 72-30.
79. Kerawala C, Roques T,Jeannon JP, Bisase B.Oral Cavity andLip Cancer :United Kingdom National Multidisplinary Guidelines.The Journal of Laryngology & Oncology 2016; 130(Suppl.S2): S83-S89.
80. Basoli ÉR, Valente VB, Mantovan B et *al*. Lip Cancer: A Cliniopathological study and Treatment outcomes in a 25-year Experience.J Oral Maxillofac Surg. 2016; 74:1360-1367.
81. Tanyeri G, Eskiizmir G. The Management, Current Treatment Modalities and Reconstruction Techniques for Lip Cancer.Turk Arch Otolaryngol 2014; 52: 22-32.

82. Alhabbab R, Johar R. Lip, Cancer prevalence, epidemiology, diagnosis, and management: A review of literature. Advances in Oral and Maxillofacial Surgery 2022: 6100376.
83. Ahmad P, Arshad AI, Jehangin M, Mahomood R,et al. Association of socio-demographic and clinicopathological risk factors with oral cancers a19 years retrospective study. Pesqui Bras Odontopediatria Clin Integ 2021; 21: e0031.
84. Rezapour A, Jatangiri R, Olyaeemanesh A,Kalagahchi B, Nouhi M, Nahvijou A. The economic burden of oral cancer in Iran. PloS ONE 2018; 13 (9): e0203059.
85. Arrangaiz ZR, Cordera F, Caba D, Moreno E, Luque de Léon and Muñoz M. Oral Tongue: Review and current Management. Cancer Rep Rev 2018; 2(3):1-9.
86. Kim YJ, Kim JH. Increasing and improving of oral tongue squamous cell carcinoma. Sci Rep 2020; 10(1):7877.
87. Ion Ciucã F(MÂRÂSESCU), Marasescu PC, Matel M, et al. Epidemiological and histological Aspects ofTongue Squamous Cell Carcinomas-Retrospective Study. Curr Health Sci J. 2018; 44(3):211-214.
88. Mailiza F, Rifani.Chronic Ulcer miming Oral Squamous Cell Carcinoma (A case report).
89. Chen CH, Chung CY, Wang LH, Lin C, Lin HL, Lin HC. Risk of cancer among HIV-infected patients from a population-based nested case-control study: implications for cancer prevention. BMC Cancer 2015; 15:133.
90. Patel JB, Shah FD, Joshi 2GM, Patel PS. Clinical significance of inflammatory mediators in the pathogenesis of oral cancer. JCan Res Ther 2016; 12: 447-57.
91. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer.J Intern Med. 2000; 248: 171-83.
92. Niklander SE. Inflammatory Mediators in Oral Cancer Pathogenic Mechanisms and Diagnostic Potential. Front Oral Health 2021; 22: 642238.
93. Shivappa N, Hebert JR, Rosayo V, Garavello W, Serraino D, La Vecchia. Inflammatory potential of diet and risk of oral and pharyngeal cancer in a large case-control study from Italy. Int J Cancer 2017; 141:471-9.
94. Jimi E, Kokabu S, Matsubara T, Nakatomi C, Matsuo K, Watanabe S. NF-kB acts as a multifunctional modulator in bone invasion by oral squamous cell carcinoma. Oral Sci Int. 2016; 13: 1-6.
95. Loiza N, Demaria M. Cellular senescence and tumor promotion: is aging the key? Biochim Biophys Acta 2016; 1865:155-67.
96. Panneer Selvam N, Sadaksharam J. Salivary interleukin-6 in the detection of oral cancer and precancer.Asia Pac J Clin Oncol. 2015; 11: 236-41.
97. Mozaffari HR, Ramezani M, Mahmoudiahmadabadi M, Omidpanah N, Saseghi M. Salivary and serum levels of tumor necrosis factor-alpha in oral lichen planus: a systematic review and meta-analysis study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017; 124:e183-9.
98. Mohamed S, Ram H, Gupta PN, Husain N, Bhatt M. Overexpression of COX-2 in oral squamous cell carcinoma patients undergoing chemo radiotherapy. Nat J Maxilloc Surg 2011; 2: 17-21.
99. Hashemi Goradel N,Najafi M, Salehi E, Farhood B, Morterzaee K. Cyclooxygenase-2 in Cancer: a review. J Cell Physiol. 2019; 234: 5683-99.
100. Mc Cormick DL, ¨Phillips JM,Horn TL, Johnson WD, Steele VE, Lubet RA. Overexpression of COX-2 in rat oral cancers and prevention of oral carcinogenesis in rats by selective and non-selective COX inhibitors. Cancer Prev Res (Philadelphia, PA) 2010; 3: 73-81.
101. Choudari SK, Chaudary M, Bagde S, Gadbail AR, Joshi V.Nitric oxide and cancer :Areview. WorldJ Surg Oncol. 2013; 11: 118.
102. Choudhari SK, Sridharan G, Gadbail A, Poornima V. Nitric oxide and oral cancer: A review. Oral Oncol. 2012; 48: 475-83.
103. Borse V, Konwar AN, Buragohaim P. Oral cancer diagnosis and perspectives in India. Sensors International 2020; 1: 100046.

104. Singh S, Halder A, Oindrila S, et al. Spectroscopic Bimolecular Recognition of Toluidine Blue: Key information Towards Development of a Non-Invasive Device for Oral Cancer Detection. Front Oncol. 2020; 10: 529132.
105. Bhosale S, Vyas T.Application of oral CDx Brush Biopsy in Oral Cancer Detection. J Dent Res Prac 2019; 1(1): 4-6.
106. Gaida K, Deuerling L, Neumann H et al. Comparison between two cell collecting methods for liquid—based brush biopsies: a consecutive and retrospective study. BMC Oral Health 2021; 2:195.
107. Fuller C, Camilon R, Nguyen S, Jennings J, Day T.and Gillespie MB. Adjunctive diagnostic techniques for oral lesions of unknown malignant potential: systematic review with meta-analysis. Head Neck 2015; 37: 755-762. doi:10.1002/head.23667.
108. Vyas T. Biopsy of oral lesions: A review article .J Adv Med Dent Scie Res 2018; 6(1): 27-35.
109. Kaczor-Urbanowicz KE, Martin Carreras-Presas C, Aro K et al. Diagnostic de la salive .vues et orientations actuelles. XP Biol Med 2017; 242(5): 459-472.
110. Khursid Z, Zafar MS, Khan R, Najeeb C, Slowey PD, Rehman IU Role oif salivary Biomarkersin Oral Cancer Detection. Adv Clin Chem. 2018; 86: 23-70.
111. Cristaldi M, Mauceri R, Di Fede O, Giuliana G, Campisi G and Panzerella V. Salivary Biomarkers for oral squamous cell carcinoma Diagnosis and Follow-up: current status and perspectives. Front Physiol. 2019. https://doi.org/10.3389/fphys.2019.01476.
112. Chu HW, Chang KP, Hsu CW, et al. Identification of salivary Biomarkers for oral cancer Detection with untargeted and targeted quantitative proteomics Approaches. Mol Cell Proteomics 2019; 18(9): 1796-1806.
113. Piyarathne NS, Rasnayake RMSGK, Angammana R et al. Diagnostic salivary biomarkers in oral cancer and oral potentially malignant disorders and their relationships to risk factors-A systematic review. Expert Review of Molecular Diagnostics 2021; 789-780. doi: 10.1080/147737159.2021.1944106.
114. Nadisha S. Piyarathne, RMSGSK Rasnayake, Randiline Angammama et al. Diagnostic salivary biomarkers in oral cancer and oral potentially malignant disorders and their relationships to risk factors-A systematic review. Expert Review of Molecular Diagnostics 2021. 21:789-807.
115. Alexandre P, Hainaut P, Guenoun A, Dinh-Phong N, Lamy JP, Guerber F, Troalen F, Jérôme AD, Boissan M. En marche vers une oncologie personnalisée : l'apport des techniques génomiques et de l'intelligence artificielle dans l'usage des biomarqueurs tumoraux circulants. Bull Cancer 2022; 109: 170–184.
116. Dikova VR, Principe S, Bagan JV.Salivary inflammatory proteins in patients with oral potentially malignant disorders. J Clin Exp Dent. 2019; 11(7): e659-64.
117. Shang C, Feng L, Gu Y, Hong H, Hong L, Hou J. Impact of MultidisciplinaryTeam Management on the Survival Rate of Head and Neck Cancer Patients: A Cohort Study Meta-analysis.Front Oncol. 2021; 11: 630906.
118. Alobaidi F, Doss J, Abmurat N. Multi-disciplinary Team (MDT) Approach in oral cancer management: An exploratory Study. Journal of Global Oncology 2018; 4(supplement 2): 96s-96s.
119. Petrovic I, Rosen EB, Matros E, Huryn JM, and Shah JP. Oral Rehabilitation of the Cancer Patient. J Surg Oncol. 2018; 117(8): 1729-1735.
120. Tuner T, Mupparapu M, Akintoye SO, Review of the complications associated with treatment of oropharyngeal cancer a guide for the dental practioner. Quintescence Int. 2013; 44: 267-79. doi:10.3290/j.qi.a29050.
121. Ketabat F, Pundir M, Muhabatpour F, Lobonova L ,Koutsopoulos S, et al. Controlled drug delivery systems for oral cancer treatment. Current status and future perspectives.Pharmaceutics 2019; 11: 302. doi: 10.3390pharmaceutics11070302.
122. Tovey P, Chatwin J, Broom A. Traditional complementary and alternative medicine and cancer care : An international analysis of grassroots integration. London, 2007 (Routledge).

123. Dong W, Xiaojie D, yuhui Z, Zhen M, Jing W. Traditional Chinese medicine for oral squamous cell carcinoma: A Bayesian network meta-analysis protocol. Medicine 2020; 99(43): e22955.
124. Wang S, Shunqin L, Wu D. Positive role of Chinese herbal medicine in cancer immune regulation. The American Journal of Chinese Medicine 2020; 48(07): 1571-1592.
125. Benali T, Khabbach A, Ennabili A, Hammani K. Ethnoparmacological prospecting of medicinal plants from the province of guercif (NE of Morocco) Moroccan J Biol. 2017; 1-14.
126. Amrati FEZ, Bourhia M, Slighoua M et al. Traditional medicinal knowledge of plants used for cancer treatment by communities of mountainous areas of Fez-Meknes-Morocco. Saudi Pharmaceutical Journal 2021; 29 :1185-1204.
127. Musial C, Kuban- Jankowska A, Gorska-Ponikowska M. Beneficial properties of green tea Catechins. Int. J. Mol. Sci. 2020; 21:1744.
128. Ramshankar V, Krishnamurthy A. Chemoprevention of oral cancer: green tea experience. Journal of Natural Science Biology and Medicine 2014; 5(1): 3-7.
129. Ganjre A, Kathariya R, Bagul N, and Pawar V. Anti-carcinogenic and anti -bacterial properties of selected spices: implications in oral health Clin Nutr Res 2015; 4(4): 209-21.
130. Nazhvani AD, Sarafraz N, Askari F, Heidari F, Razmkhah M. Anti-Cancer Effects of Traditional Medicina Herbs on Oral Squamous Cell Carcinoma. Asian Pac J Cancer Prev. 2020; 21(2): 479-484.
131. Wang W, WYang Y, Zhang W, Wu W. Association between coffee consumption and the risk of oral cancer: a meta-analysis of observational studies. Int. J Clin Exp Med 2015; 8 :116-65.
132. Yue E, Tuguzbaeva G, Qin Y, Li A et al. Anthocyanin is involved in the activaction of pyroptosis in oral squamous cell carcinoma. Phytomedecine 2019; 56: 286694.
133. Siverman S, Kerr AR, Epstein JB. Oral and pharyngeal cancer control and early Detection. J. Cancer Educ. 2010; 25: 279-281.
134. Wanakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009; 45: 309-316.
135. Ghani WWN, Ramathan A, Prime SS et al. Survival of oral cancer patients in different ethnicities.Cancer Invest. 2018; 37(7): 275-287.
136. Capote-Moreno A, Brabyn P, Muñoz-Guerra MF et al. Oral squamous cell carcinoma: epidemiological study and risk factors assessment based on 39-year series. Int J Oral Maxillofac Surg. 2020; 49(12):1525-1534.).
137. Johnson NW, Warnakulasuriya S,Gupta PC et al. Global Oral Health inequalities in incidence and outcomes for oral cancer: causes and solutions. Advances in Dental Research 2011; 23(2): 237-46.