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Etiology, Epidemiology and Pathophysiology of Oral Squamous Cell Carcinoma: A Review Article

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity. It accounts for more than 90% of oral cancers and is ranked as the sixth most prevalent cancer when considered on a global scale. In terms of pathogenesis, genetic, epigenetic, and environmental factors play a role in their interaction. Well-established risk factors are smoked tobacco, alcohol drinking, betel quid chewing, and high-risk human papillomavirus (HPV) infection-especially HPV-16. From these exposures mutate key oncogenes and tumor suppressor genes such as RAS, MYC, and TP53 plus promoter hypermethylation of genes like p16 and DAPK.These molecular changes lead to unrestrained cell proliferation apoptosis inhibition angiogenesis and tissue invasion facilitated by matrix metalloproteinases (MMPs). Geographically, OSCC varies a lot. The cultural practice of chewing betel quid in South and Southeast Asia makes this region the highest implac6tion for this disease, while lower rates are seen in Arab countries as alcohol consumption is not prevalent. In Iraq, increasing tobacco consumption, more waterpipe (shisha) smoking, and lifestyle changes have driven an upward trend of OSCC incidence. It usually affects men above the age of 40; however, recent data show increasing incidence among the younger nonsmokers which may indicate a shift in etiology where HPV infection plays a bigger role. Genetic studies in global and Iraqi populations have shown consistent overexpression of p53, cyclin D1, and EGFR. Conserved molecular pathways because of regional exposure differences. The survival rate remains poor due to late-stage diagnosis and recurrences. To improve patient outcomes in the face of these challenges will require culturally sensitive public health campaigns, early detection facilitated by molecular biomarkers, and targeted therapies that genetic profiling guides. This review synthesizes available evidence on the etiology and epidemiology of OSCC, highlighting gaps in knowledge and proposing avenues for research that can help direct preventive efforts while decreasing this disease's burden globally.

KEYWORDS
Etiology, Epidemiology, pathophysiology, OSCC,

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a malignant neoplasm of the oral cavity; more than 90% of intraoral cancers are reported to be squamous cell carcinomas (Warnakulasuriya, 2009). Clinically, OSCC presents as non-healing ulcers or exophytic masses; it can at times manifest through mucosal lesions like leukoplakia and erythroplakia involving high-risk sites—tongue, floor of the mouth, buccal mucosa, gingiva—unusually in any part of the mucosa (Scully & Bagan, 2009). In the last few decades, even though there has been a significant evolution in surgery as well as radiotherapy and chemotherapeutic approaches, stagnant figures regarding five-year survival rates carry an implicit message—the majority of cases continue to be diagnosed at late stages with additional recurrences being noted (Gupta et al., 2013).

Though broad research has largely identified the risk factors, leading to a good deal of prevention in some parts of the world, knowledge gaps that are essentially critical remain. Not least among them is that troubling epidemiological trend—the increasing incidence of OSCC in younger adults who, by and large, do not have traditional risk factors such as tobacco or alcohol exposure. This change underlines the importance of focused epidemiological studies to further understand alternative etiological pathways—notably genetic susceptibility and viral impacts that may be emerging along with other environmental influences.

While the link between HPV infection and OSCC has become more evident, the exact molecular pathways through which HPV facilitates malignant transformation in oral tissues remain largely speculative (Gillison et al., 2000). Targeted treatment and predictive biomarkers would emerge from the elucidation of these mechanisms. Moreover, strong-qualitative longitudinal research on how effective the long-term implementation of preventive strategies, including HPV vaccination programs plus broad tobacco cessation efforts-in different populations and cultural settings is urgently needed (Warnakulasuriya, 2009). That study needs to ascertain if such interventions translate into measurable decreases in both incidence and mortality of OSCC would fill those knowledge gaps to advance not only more robust public health policies to reduce this global burden but also scientific understanding about its pathogenesis.

Pathophysiology of OSCC

The Oral squamous cell carcinoma(OSCC) develops through a multitude of steps and factors, genetic, epigenetic, and environmental changes responsible for the transformation of normal oral epithelium into invasive malignancy (Warnakulasuriya, 2009). At the molecular level, it begins with genetic alterations that occur in activating mutations of oncogenes such as RAS and MYC and inactivating mutations or deletions of tumor suppressor genes like TP53. These are common in OSCC(Leemans et al., 2018). The disruption of normal cellular mechanisms controlling the cell cycle allows for unregulated cellular proliferation to take hold. Apoptosis is also disregarded, and invasive capabilities are acquired. In terms of histopathology, most cases of OSCC develop from potentially malignant disorders—leukoplakia and erythroplakia —through an epithelial hyperplasia stage through dysplasia into carcinoma in situ before finally reaching invasive carcinoma (Warnakulasuriya, 2009).

Growth continues to require new blood vessel formation largely driven by VEGF, and surrounding tissues breaking down by enzymes like MMPs (particularly MMP-2 and MMP-9) that help in local invasion as well as metastatic spread (Giacomini et al., 2020). In the world, well-known risk factors—for example, using tobacco, drinking too much alcohol, and infection with high-risk types of the human papillomavirus (HPV)—trigger these molecular events along with making them worse through constant inflammation; damage to DNA caused by oxidation; and direct insertion of viral oncogenes into the host genome. In Iraq and other Arab nations, cultural and lifestyle factors mold the etiological landscape of OSCC. Tobacco in the form of smoking and smokeless products such as shammah and toombak are great carcinogens; alcohol is relatively a minor contributor due to cultural restrictions. It has also recently gained entry as an important growing risk factor, that is waterpipe (shisha) smoking which delivers high concentrations of carcinogenic compounds responsible for generalized epithelial alterations— field cancerization.

Other local contributing factors include chronic mechanical irritation from poor oral hygiene, dentures that do not fit well, or trauma to the teeth. This sets up an inflammatory environment around the area that eventually helps malignant transformation develop (Al-Attas et al., 2014). Molecular studies done within Iraqi and Arab populations displayed overexpression of p53,

cyclin D1, and epidermal growth factor receptor (EGFR), indicating that although environmental exposures may differ, the primary pathophysiological mechanisms are conserved to a great extent with what has been noted globally (Abdulrahman et al., 2022). Newer research also brings to light the major role played by epigenetic changes such as hypermethylation of promoters of tumor suppressor genes wherein critical regulatory pathways can be rendered silent and carcinogenesis brought about in an accelerated manner Leemans et al., 2018). These molecular interplays combined with environmental interactions need a more in-depth study to drive preventive strategies specific to regions, early diagnostic markers, as well as targeted therapeutic interventions for OSCC.

Epidemiology of OSCC

Oral squamous cell carcinoma, the 6th most prevalent cancer globally, is responsible for more than 350,000 new cases and over 177,000 deaths annually (Bray et al., 2018). In terms of the overall burden of the disease, this cancer displays geographic variation at a global scale as cultural habits in lifestyle choices play an important role in exposure to established risk factors for the malignancy. The highest incidence rates are documented from South and Southeast Asia where chewing betel quid with areca nut along with different forms of smokeless tobacco contribute carcinogens (Gupta et al., 2013). Elsewhere particularly Western countries etiologies prevail through a combination of cigarette smoking and excessive alcohol consumption along with infection by high-risk types of human papillomavirus one of which is HPV-16(Warnakulasuriya,2009).

The prevalence of OSCC in Arab countries, including Iraq, is not as prominent as in the leading regions; however, data indicate a slow ascending trend. This is due to increased tobacco usage and the more popular waterpipe (shisha) smoking, along with other lifestyle habits taken from urbanization and globalization trends (Al-Attas et al., 2014; Abdullah et al., 2018). In Iraq, this cancer ranks first among oral malignancies. It most commonly occurs above 40 years in males and the tongue and buccal mucosa are reported as the most frequent sites (Abdulrahman et al., 2022). In Iraq, this cancer's age-standardized incidence rate be around 2.5-3.0 per 100,000 population which is lower than the average of the world but has been increasing consistently for better part of last two decades.

Norms, both cultural and religious, which means that alcohol consumption is not embraced in most Arab countries may explain the lower incidences of OSCC compared to those of Western countries. However, this does not diminish the fact that there is a major public health challenge with improved and more expanded forms of tobacco use-including smokeless tobacco such as shammah and toombak—as well as increasing waterpipe smoking (Al-Attas et al., 2014). The pattern gives an indication that public health interventions in that region should demand reforms at the most emergent levels to change behavior, supported by early detection programs and educational campaigns addressing risk reduction as well as improving early diagnosis for better patient outcomes (Warnakulasuriya, 2009).

The emerging epidemiological trends also mean demographic shifts in the incidence of OSCC. For example, Patel et al. in 2011 noted a disturbing increase between 18 and 44 years of age in oral tongue squamous cell carcinoma (OTSCC) for young white women in the United States; this suggested new, maybe non-conventional risk factors that deserved more exploration. This fits with more general patterns seen with head and neck squamous cell carcinomas (HNSCC), which have been diagnosed more frequently among younger people worldwide; partly this was blamed on lifestyle changes and HPV infections. Barsouk et al., reaffirmed that the trend of incidence for OSCC is still increasing globally with tobacco use and alcohol consumption; hence comprehensive public health policies are critically needed. These challenges are further compounded by the increasing incidence of HPV-positive HNSCC, which has now become a major sub-division of cases and hence underscores the need for the inclusion of HPV vaccination and specific screening as components in the strategies for OSCC prevention (Gillison et al., 2015). Data thus far illustrating this sort of complex, shifting epidemiological landscape that calls for multi-pronged, evidence-informed interventions responsive to local and global contexts.

Etiological Factors

Oral squamous cell carcinoma (OSCC) develops from multifactorial etiologies, where dynamic interactions occur between environmental exposures, viral infections, and genetic predispositions. However, in most cases the etiology of OSCC is attributed to tobacco

smoking and alcohol consumption because these two provide documented synergistic carcinogenic effects with high potentiality (Gupta et al., 2013). In South and Southeast Asia habitual chewing of betel quid and areca nut add substantially to the incidence of OSCC majorly through chronic irritation of the mucosa, it also produces reactive oxygen species that damage the DNA of epithelial cells Gupta et al., 2013). Chronic trauma not only from sharp teeth but also ill-fitting dentures combined with poor oral hygiene create inflammatory microenvironments about which carcinogenesis can take place (Warnakulasuriya, 2009).

Increasingly, high-risk HPV infections—most notably HPV-16—are considered etiological agents, particularly in OSCC emerging among younger patients and nonsmokers (Gillison et al., 2000). This has caused a significant change in the classic risk profile because viral oncogenes like E6 and E7 act to disable tumor suppressor proteins p53 and Rb, adding to cell proliferation and malignant transformation (Jerjes et al., 2010). Low fruit and vegetable consumption does not provide antioxidant defense against mucosal protection related to carcinogenic assault; hence deficiency is also reported to associate with increased risk of OSCC (Warnakulasuriya, 2009). The battle humanely toward better diagnostic and therapeutic strategies notwithstanding, however, the five-year survival rate is still about 50% with OSCC due to late presentation and the tumors propensity for recurrence or metastasis (Scully & Bagan, 2009).

In terms of causative agents for carcinomas, tobacco remains the most prevalent in causing OCSSNg et al. (2017) described specific molecular mechanisms through which nitrosamines and reactive metabolites, derived from tobacco, cause genetic mutations and epigenetic changes important in oncogenesis. This rising trend of HPV-positive OSCC in young people also emphasizes changing etiological factors in OSCCJerjes et al., 2010). According to Johnson et al.(2011), to reframe epidemiological models and design new ways to prevent the disease that is specific to this pathosystem, a nuanced understanding should encompass all these different risk factors—conditions of environment—and viral infection.

Lifestyle factors are important in the role of alcohol overconsumption, diet, and emerging habits one of which is waterpipe (shisha) smoking. Barsouk et al. (2023) have indicated that these factors play a role as they interact with very complex mechanisms both in disease causation and treatment outcome. This calls for detailed epidemiological investigations that can isolate the relative contribution of each factor to guide intervention strategies within specific cultures. Genetically, OSCC pathogenesis manifests changes in controlling genes. Mutated tumor suppressor genes such as TP53 on a large scale; globally, addition of oncogenes like CCND1 (which codes for cyclin D1) and amplified growth pathways through EGFR enlargement all together disturb control of the cell cycle alongside with programmed cell death thereby supporting transformation into malignancy. (Gupta et al., 2013; Leemans et al., 2018) Epigenetic changes also help by promoting hypermethylation p16 , DAPK and other critical checkpoint gene promoters.(Leemans et al., 2018)

In Iraq and other Arab countries, limited molecular studies have suggested the existence of such a pathogenic pathway since overexpression of p53 and cyclin D1 in OSCC specimens was reported to be in accordance with trends all over the world (Abdulrahman et al., 2022). The regional exposures—as an example, smokeless tobacco (shammah and toombak), waterpipe smoking, and chronic mucosal irritation—are most likely to compound these genetic changes making those individual more susceptible (Idris et al., 1998; Al-Attas et al., 2014). It is this merging of common mechanisms with region-specific ones that underlines the potential value of genetic and molecular profiling being integrated into screening as well as personalized therapeutic strategies in a drive towards improved prevention of OSCC and better outcomes for patients all around the world..

CONCLUSION

In summary, oral squamous cell carcinoma remains the predominant cancer type affecting the world's population. The initiation and development of this malignancy involve a myriad of genetic, epigenetic and environmental risk factors. Its incidence is strongly geographic, cultural behaviours, lifestyle habits and emerging influences such as HPV infection define numerous other cases. The low survival rate still stands out as an indicator of late-stage presentation and high recurrence notwithstanding the strides made in research. These should go hand in hand with culturally adapted public health campaigns, early detection supported by molecular biomarkers, and targeted

therapies based on genetic profiling to improve overall outcomes. In addition to that, more comprehensive research concerning region-specific risk factors demographic changes in molecular pathogenesis will be crucial for future development in effective prevention strategies screening methods and treatment options For that reason addressing these gaps can help future research drive a change not only globally but regionally where OSCC is endemic improving patient prognosis as well as quality of life.

REFERENCES

1. Abdullah, R., Ali, A. A., & Abed, H. (2018). The incidence and pattern of oral cancer in Iraq from 2002 to 2015. Journal of Cancer Prevention, 23(2), 99–106. https://doi.org/10.15430/JCP.2018.23.2.99
2. Abdulrahman, S., Al-Nuaimi, A. S., & Ali, I. (2022). Oral cancer in Iraq: a retrospective analysis of 20 years. Journal of Oral and Maxillofacial Pathology, 26(1), 83–88. https://doi.org/10.4103/jomfp.jomfp_111_21
3. Abnet, C.., Arnold, M.., & Wei, Wenqiang. (2017). Epidemiology of Esophageal Squamous Cell Carcinoma.. *Gastroenterology* , 154 2 , 360-373 . http://doi.org/10.1053/j.gastro.2017.08.023
4. Akl, E. A., Gaddam, S., Gunukula, S. K., Honeine, R., Jaoude, P. A., & Irani, J. (2011). The effects of waterpipe tobacco smoking on health outcomes: a systematic review. International Journal of Epidemiology, 39(3), 834–857. https://doi.org/10.1093/ije/dyq167
5. Al-Attas, S. A., Ibrahim, S. S., Amer, H. A., Darwish, Z. E., & Hassan, M. H. (2014). Prevalence of oral cancer risk factors among patients attending outpatient dental clinics in Saudi Arabia. Asian Pacific Journal of Cancer Prevention, 15(1), 318–321. https://doi.org/10.7314/APJCP.2014.15.1.318
6. Barsouk, A.., Aluru, J.., Rawla, Prashanth., Saginala, Kalyan., & Barsouk, Alexander. (2023). Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. *Medical Sciences* , 11 . http://doi.org/10.3390/medsci11020042
7. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68(6), 394–424. https://doi.org/10.3322/caac.21492
8. Giacomini, T., Mozzillo, R., & Caraglia, M. (2020). Molecular mechanisms in oral squamous cell carcinoma: Role of angiogenesis and matrix metalloproteinases. Cancers, 12(8), 2195. https://doi.org/10.3390/cancers12082195
9. Gillison, M. L., Koch, W. M., Capone, R. B., Spafford, M., Westra, W. H., Wu, L., ... & Sidransky, D. (2000). Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. Journal of the National Cancer Institute, 92(9), 709–720. https://doi.org/10.1093/jnci/92.9.709
10. Gillison, M.., Chaturvedi, A.., Anderson, W.., & Fakhry, C.. (2015). Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma.. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* , 33 29 , 3235-42 . http://doi.org/10.1200/JCO.2015.61.6995
11. Gupta, B., Johnson, N. W., & Kumar, N. (2013). Global epidemiology of head and neck cancers: a continuing challenge. Oncology, 85(4), 223–230. https://doi.org/10.1159/000353627
12. Idris, A. M., Ibrahim, S. O., Vasstrand, E. N., Johannessen, A. C., Lillehaug, J. R., Magnusson, B., & Nilsen, R. (1998). The Swedish snus and the Sudanese toombak: are they different? Oral Oncology, 34(6), 558–566. https://doi.org/10.1016/S1368-8375(98)00038-8
13. Jerjes, W.., Upile, T.., Petrie, A.., Riskalla, A.., Hamdoon, Z.., Vourvachis, M.., Karavidas, K.., Jay, A.., Sandison, A.., Thomas, G.., Kalavrezos, N.., & Hopper, C.. (2010). Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. *Head & Neck Oncology* , 2 , 9 - 9 . http://doi.org/10.1186/1758-3284-2-9
14. Johnson, N.., Jayasekara, P.., & Amarasinghe, A.. (2011). Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology.. *Periodontology 2000* , 57 1 , 19-37 . http://doi.org/10.1111/j.1600-0757.2011.00401.x
15. Leemans, C. R., Snijders, P. J. F., & Brakenhoff, R. H. (2020). Head and neck squamous cell carcinoma. Nature Reviews Disease Primers, 6(1), Article 92. https://doi.org/10.1038/s41572-020-00233-2

16. Leemans, C. R., Snijders, P. J., & Brakenhoff, R. H. (2018). The molecular landscape of head and neck cancer. Nature Reviews Cancer, 18(5), 269–282. https://doi.org/10.1038/nrc.2018.11

17. Ng, Jia-Hui., Iyer, N.., Tan, M.., & Edgren, G.. (2017). Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. *Head & Neck* , 39 . http://doi.org/10.1002/hed.24589

18. Patel, Sagar C., Carpenter, W.., Tyree, S.., Couch, M.., Weissler, M.., Hackman, T.., Hayes, D.., Shores, C.., & Chera, B.. (2011). Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years.. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* , 29 11 , 1488-94 . http://doi.org/10.1200/JCO.2010.31.7883

19. Scully, C., & Bagan, J. (2009). Oral squamous cell carcinoma overview. Oral Oncology, 45(4–5), 301–308. https://doi.org/10.1016/j.oraloncology.2008.05.016

20. Scully, C., & Bagan, J. (2009). Oral squamous cell carcinoma overview. Oral Oncology, 45(4–5), 301–308. https://doi.org/10.1016/j.oraloncology.2008.05.016

21. Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. Oral Oncology, 45(4–5), 309–316. https://doi.org/10.1016/j.oraloncology.2008.06.002