International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 06, 2020
ISSN: 1475-7192

ETIOLOGY AND REGIONAL VARIATION OF ORAL CANCER- A REVIEW

[1]Paras Ahmad, [2]Mohmed Isaqali Karobari, [3]Rizwan Mahmood, [4]Tang Liszen, [5]*Jawaad Ahmed Asif

***ABSTRACT**--The American National Cancer Institute (National Cancer Institute, 2009), given the classification of cancer, can be classified into five primary types including central nervous system cancers, sarcomas, leukaemias, carcinomas, myelomas and lymphomas. The most common type of cancer which covers external and internal cell surfaces arising for the cell is carcinoma, i.e., mouth, lung, breast and colon. The confirmed primary known oral cancer risk factors are tobacco consumption and alcohol intake: it is believed that about 75% of head and neck cancers are associated with these habits. Other risk factors include betel quid chewing, infection with HPV, genetics, and radiation.*

***Keywords**-- Carcinoma, Genetic, Leukaemia, Lymphomas, and Myeloma*

I. INTRODUCTION

Cancer is an unchecked growth of cells due to an imbalance between apoptosis and cell division [1]. According to the World Health Organization (WHO), cancer is a disease caused by inherited and somatic mutations in genes known as tumor suppressor genes (TSG) and oncogenes. Under normal circumstances, old and damaged cells are replaced by new cells. However, during cancer, the cell's DNA is damaged or altered, causing mutations, thus influencing the growth of the cell. A tumor can be categorized either as malignant or benign. A malignant tumor could spread to nearby tissues (local invasion) as well as other parts of the body (metastasis). A benign tumor is localized and does not spread to other parts of the body [2].

According to the American National Cancer Institute, cancer can be classified into five primary types, including central nervous system cancers, sarcomas, leukemias, carcinomas, myelomas, and lymphomas. Cancers of the central nervous system arise from tissues of the spinal cord and brain. Sarcomas arise from the supportive tissues which constitute bone, cartilage, blood vessels, fat, connective tissues, and muscle. Leukemia is an immature blood cell cancer that arises from the bone marrow and can accumulate in abundant quantity in the bloodstream. The most common type of cancer which covers external and internal cell surfaces arising for the cell

[1] *Oral Medicine Unit, School of Dental Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.*

[2] *Conservative Dentistry Unit, School of Dental Sciences, Universiti Sains Malaysia, Health campus, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.*

[3] *Oral Medicine Unit, School of Dental Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.*

[4] *Oral and Maxillofacial Surgery Unit, School of Dental Sciences, Universiti Sains Malaysia, Health campus, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia.*

[5] **Oral and Maxillofacial Surgery Unit, School of Dental Sciences, Universiti Sains Malaysia, Health campus, 16150 Kubang Kerian, Kota Bharu, Kelantan, Malaysia, dentistjawaad@gmail.com, Mobile : +60 11 25845771*

Received: 22 Feb 2020 | Revised: 13 Mar 2020 | Accepted: 05 Apr 2020

is carcinoma, i.e., mouth, lung, breast, and colon. Myeloma and lymphoma arise from cells and lymph nodes present in the human immune systems. The development of cancer requires multiple genetic alterations affected by genetic predisposition and vulnerability to environmental carcinogens such as tobacco smoking, alcohol consumption, viral infection, and chronic inflammation [3].

II. ETIOLOGY OF ORAL CANCER

Oral cancer results from mutations in the DNA that can affect different genes and increases due to various risk factors (Figure 1). The confirmed primary known oral cancer risk factors are tobacco consumption and alcohol intake: it is believed that about 75% of head and neck cancers are associated with these habits. Other risk factors include betel quid chewing, infection with HPV, genetics, and radiation [4].

2.1 Use of Tobacco

2.1.1 Smoking:

In Asian countries, tobacco use is widespread [5]. The use of tobacco products has been reported in more than 90% of oral cancer cases. Tobacco is an independent factor and a relative risk factor for oral cancer. The oral cancer occurrence in tobacco users is 11 times higher than those who have never used tobacco [6]. Over 300 carcinogens have been identified to be contained within tobacco smoke, which readily dissolve in saliva [7]. These include the polycyclic aromatic hydrocarbon, such as benzpyrene and the tobacco-specific N-nitrosamines, including four (methylnitrosamino) -1- 3- (3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN) [8]. These carcinogens are produced when the tobacco is lit and moderately from some smokeless tobacco. These carcinogens are readily absorbed into the oral mucosa and then cause to replicating cells. The potent addictive chemical in tobacco is nicotine; however, the main carcinogens are in other components of the tobacco leaf. Most of the nicotine absorbed across the epithelium of the oral mucosa is metabolized in the liver and is eliminated via renal excretion. In the brain, it binds to nicotinic acetylcholine receptors (nAChRs) [9]. This binding is associated with the rewarding effects of nicotine. Receptor adaption happens in reaction to chronic exposure with dopamine release, which causes dependence and withdrawal reactions [10]. While nicotine is a potent addictive chemical in tobacco, its potential carcinogenic role is still unclear. However, there is an on-going debate based on animal and theoretical studies to determine its exact cancer-inducing potential [11].

2.1.2 Smokeless Tobacco

According to International Head and Neck Cancer Epidemiology [12] confederation analyses of smokeless tobacco – either as tobacco chewing or powdered snuff – a higher risk association for oral cancer was found, with an approximately double risk even among individuals who never smoked a cigarette [13]. Thus, smokeless tobacco cannot be regarded as a risk reduction alternative.

2.1.3 Alcohol consumption

Alcohol consumption is considered as an important risk factor for oral cancer. Beer is more common in Turkey, Indonesia, Myanmar, and Malaysia, whereas spirits are more frequently used in India, Nepal, Sri Lanka, Bangladesh, China, Pakistan, and Thailand [14]. It is not alcohol but its first metabolite, acetaldehyde, which is

the most vital carcinogen. Now, no limit is considered safe for alcohol intake. The INHANCE consortium comprised of 35 studies with 25,500 oral carcinoma cases and 37,100 controls. Alcohol consumption among non-smokers contributed as a significant risk among those who consumed more than glasses per day. The benefit of quitting alcohol consumption was only noticeable after 20 years. The consumption of 30 glasses or more per week inflicted a risk of 5.44 (95% CI: 3.1 – 9.2) in beer, 3.64 (95% CI: 2.2 – 5.8) in spirit and 6.3 (95% CI: 2.2 – 18.6) in wine consumers. The deleterious effects were evident in individuals who consumed high levels of alcohol rather than less quantity for a longer duration on the contrary to smokers [15].

2.1.4 Alcohol consumption and tobacco smoking (Double Trouble)

Alcohol intake and tobacco smoking are confirmed risk factors for oral cancer [16]. There was a double estimate of risk factor for oral cancer Amongst non-alcoholic smokers, the one who never consume alcohol, which escalated with the duration and frequency of smoking. Similarly risk increased two-folds in individuals consuming three or more serving of alcohol per day even though they never smoked tobacco [17]. A five times higher risk was evident in individuals with a combined habit of tobacco smoking and heavy alcohol consumption [18]. The association of strong dose-response with oral cancer risk was demonstrated by INHANCE data, with an increasing duration and frequency of alcohol intake and tobacco smoking. The risk of developing oral cancer with tobacco smoking is dose-dependent, whereas for alcohol, it is frequency-dependent [16].

2.1.5 Betel nut quid chewing

Betel nut quid, also called "paan," is a combination of substances that includes areca nut and slaked lime with tobacco or without encased in a green leaf (betel leaf) and placed in the mouth [19]. It is common in Southeast Asia and South Asia [20, 21]. According to a meta-analysis and systematic review conducted with 15 case-control cases, betel quid has been revealed to have an almost three times greater risk associated with oral cancer [19]. The WHO study showed that 60% of oral cancers might be related to chronic use of betel quid, which is closely associated with the oral erythema, oral leucoplakia, and oral submucosal fibrosis, which are potentially malignant oral lesions [22].

2.1.6 Human papillomavirus

Oral human papillomavirus (HPV) is predominantly related with oropharyngeal carcinoma risk instead of oral cancer [16]. Over 100 HPV types have been identified, but HPV 16 and 18 subtypes are the major high-risk oncogenic types [23]. A substantial increase in the risk of oropharyngeal cancer (up to 15 times greater) has been identified in people with HPV 16 as in the revolutionary 2007 *New England Journal of Medicine* [24].

Sexual transmission of Oral HPV is reported [23]. Literature has also indicate a slight increase in the risk of oropharyngeal cancer with sexual partners six or more lifelong, four or more oral sexual partners throughout life, and an early age (<16 years) of sexual introduction [25]. A meta-analysis, which included 5,396 cases of oropharyngeal carcinoma, showed increases of 72.2% after 2005 when compared with 40.5% before 2000, with considerable hikes observed in Europe and North America [26]. A recent international case-control multicentre research found proportions of cases of oropharyngeal cancer with positive HPV of 60% US and 31% in Europe (data collected in cases diagnosed in 2002-2004) [27]. This agrees with earlier estimates of an attributable fraction

of the population of about 30% in Europe [28]. Therefore, given the epidemiological trends of fast hike in oropharyngeal cancer, it appears sensible to hypothesize that the attributable quantity (in Europe and the UK) is escalating from about 1/3rd of cases and is feasibly reaching the US which is about two-thirds. It is notable (also from US data) that the etiological portion for other head and neck cancers is remarkably lower, perhaps even 3% lower for oral cancer [23].

2.1.7 Genetics

Some risk associations related to oral cancer have been identified, such as genetic variants linked with DNA repair mechanisms, alcohol metabolism, and nicotine metabolism associated genes [12]. Literature suggested a higher risk associated with having a first degree relative with oral and pharyngeal cancer [29]. A past family history of oral cancer is a potent determinant of oral cancer risk, irrespective of alcohol, and tobacco use [30]. According to a study, an almost doubled risk (70% increase) was observed in the individuals having any sibling with oral cancer. In rare inherited disorder, including xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anemia, Bloom syndrome and dyskeratosis congenital, there is a defect in caretaker genes which may result in an increase in primary malignancies [31].

2.1.8 Socioeconomic status

The other significant risk factors identified, such as alcohol and smoking in relation to the magnitude (double increase in risk), was low income and low education, socioeconomic quality [32]. This risk factor is not fully explained, but it can be linked with the quality and alcohol and tobacco used in fulfilling the urge. Poor socioeconomic status is directly related to occupations such as farmers, pesticide sprayers, and industrial laborers, where they are exposed to intense sunlight and strong chemicals. Thus, these factors influence risk behaviours; therefore, it can be categorized as "The cause of the cause" [32].

2.1.9 Oral health

The risks linked with poor oral hygiene have also initiated to be clarified by analysing the INHANCE dataset. After adjustment of alcohol and tobacco consumption, regular dental care, few missing teeth, and regular tooth brushing can significantly reduce the risk of oral cancer, but the use of a prosthesis (denture) has not been associated with increases risk [33]. The prolonged use of mouthwash (twice a day for more than 35 years) has shown slightly increase risk [15]. A recent systematic review reported non-significant higher risk associations for daily use of mouthwash [34].

2.1.10 Diet

There has been limited new evidence regarding dietary factors as well as confirming the high consumption of fresh vegetables and fruits was associated with alleviating the risk of oral cancer [35]. Interestingly, unlike many cancers [36], obesity was not associated with a high risk of oral cancer. contrastingly, literature suggest that oral cancer was more common in young people with low body mass index (BMI) (aged 30 or under) [37].

2.1.11 Young people

It is interesting to note that the risk factors previously reported was generally constant in all age groups (and indeed in the sexes), and the main risk factors observed among young adults were alcohol consumption and tobacco smoking [38].

III. REGIONAL VARIATIONS

3.1 Global burden and trends

According to the most recent peer-reviewed data by the World Health Organization International Agency for Research on Cancer (WHO IARC), 665,093 cases of oral cancers were newly diagnosed in 2018 [39]. Globally, the estimated number of deaths from the lip and oral cavity cancers were 199,560. The global estimated age-standardized risk was 2.7 per 100,000 with south-central Asia having the largest proportion (48.7%), and men being higher in experiencing oral cancers compare to women (M: F rate ratio 2:1) [39]. Worldwide, a series of comprehensive epidemiological surveys have been initiated [40]. Incidence rates of oral cancer have been increasing in women and decreasing or flat lining in men globally [41]. These changing trends are a global phenomenon and have been related to changing population risk factors. This has been described as controlling a tobacco epidemic while a human papillomavirus epidemic emerges [42]. Figure 2

Internationally, The twelfth most common cause of cancer-related mortality amongst males and sixteenth amongst females is oral cancer. Furthermore, there are marked variation geographically, for example, oral cancer in Srilankans is leading amongst men, sixth amongst women, and second overall (Figure 3). The registration to overall death ratio marked from the above numbers, i.e., R: D = 0.48, is constant with less than 50% with an average 5-year survival rate, Early diagnosis and proper multidisciplinary teams providing patient care will improve patients to do much better. Sadly, which is not the case around the world, , except for the cancers related to HPV. The predominantly diseases amongst poor are oral and other head and neck cancers: Johnson et al revealed the inequalities and contributing factor [43]. The incidence of cancer arising at sub-sites of the oral cavity and pharynx has shown wide geographical variation, depending on dominant behavioural risk factors within particular cultures. For example, alcohol is related to the tongue and floor of the mouth, betel nut quid chewing affects buccal and retro-molar sites, and sexually transmitted HPV related cancers are found mostly in the tonsil and base of the tongue [44].

3.1.1 Asia

In Asia, oral cancer is the 11th most common cancer and occupies 8th rank among all the cancers in men. In 2018, in Asia, 305,995 new male cases and 123,668 new female cases of oral cancers had been reported making a total of 429,663 new cases. The estimated number of deaths that occurred in 2018 due to oral cancers was 254,068 (182,594 males + 71,474 females), with the ASIR being 3.8 [45].

In South Asian countries, including Sri Lanka, Pakistan, India, and Bangladesh, 33% of all the cancers reported are oral cancers [46]. Tobacco consumption in various forms is the main risk factor in about 90% of oral cancers. According to the Global Burden of Cancer Study (GLOBOCAN) 2018 data, Sri Lanka has the highest

ASIR in South Asia, i.e., 10.3 and oral cancer is the most common cancer among men in Sri Lanka. The second highest ASIR in South Asia is of Pakistan, i.e., 9.3 [45].

3.1.2 Africa

A dearth of quality data has been reported in Africa, and the only available data is from a few hospital-based cancer registries. According to GLOBOCAN 2018 data, oral cancer is the 15th most common cancer in Africa. In 2018, in Africa, 19,213 new male cases and 13,250 new female cases of oral cancers had been reported making a total of 32,463 new cases. The estimated number of deaths that occurred in 2018 due to oral cancers was 20,568 (12,304 males + 8,264 females), with the ASIR being 2.6 per 100,000 populations.

3.1.3 Europe and the European Union

In 2018, in Europe, 71,911 new male cases and 33,447 new female cases of oral cancers had been reported making a total of 105,358 new cases. The estimated number of deaths that occurred in 2018 due to oral cancers was 40,342 (41,385 males + 11,774 females). A low incidence of oral cancers among males was reported in Iceland and Cyprus, whereas a high incidence was reported in Germany and the Russian Federation. The peak estimated ASIRs among females have been reported in Hungary and Denmark and among males in Hungary and France [47].

3.1.4 America

In America, oral cancer is the 11th most common cancer and constitutes 2% of all malignancies in women and 3% in men [48]. The estimated new cases for oral cancers in 2018 are 91,078 (64,319 males + 26,759 females). The estimated number of deaths that occurred in 2018 due to oral cancers was 28,568 (21,022 males + 7,546 females). Oral cancer is the 12th and 13th most common cancer in Canada and Mexico, respectively, with the ASIR in Mexico and Canada being 3.1 and 4.2, respectively (Jacobs *et al.*, 2019). In Brazil, the 7th most common cancer is oral cancer, with the ASIR being 7.2 per 100,000 populations.

3.1.5 Oceania

According to GLOBOCAN 2018 data, oral cancer is the 12th most common cancer in Oceania. In 2018, in Oceania, 4,478 new male cases and 2,053 new female cases of oral cancers had been reported making a total of 6,531 new cases. The estimated number of deaths that occurred in 2018 due to oral cancers was 1,803 (1,269 males + 534 females), with the ASIR being 7.4 per 100,000 populations. In Australia, the 9th most common cancer among men is oral cancer, with the ASIR being 8.8. In New Zealand, it is the 14th most common cancer among men, with the ASIR being 5.4. A high prevalence of oral cancer has been reported in Solomon Islands and Papa New Guinea due to betel quid chewing and tobacco smoking.

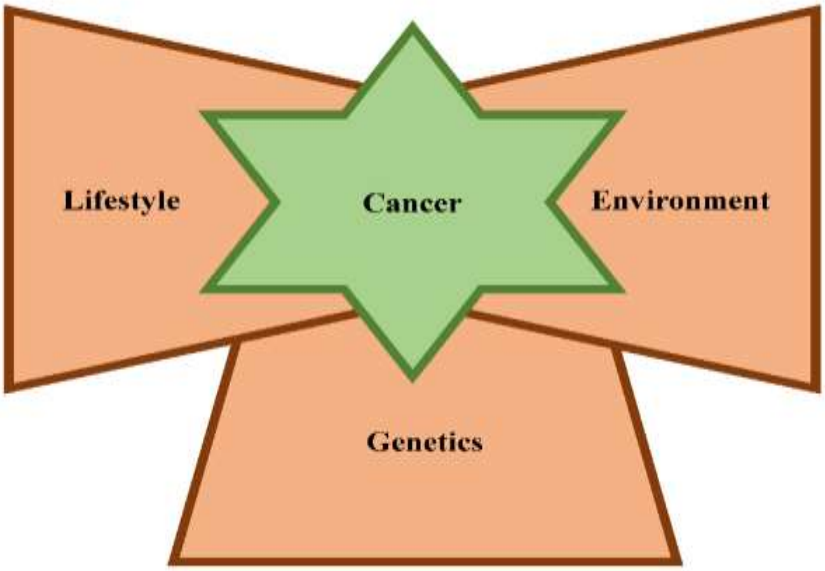

Figure 1: Cancer is mainly related to lifestyle factors.

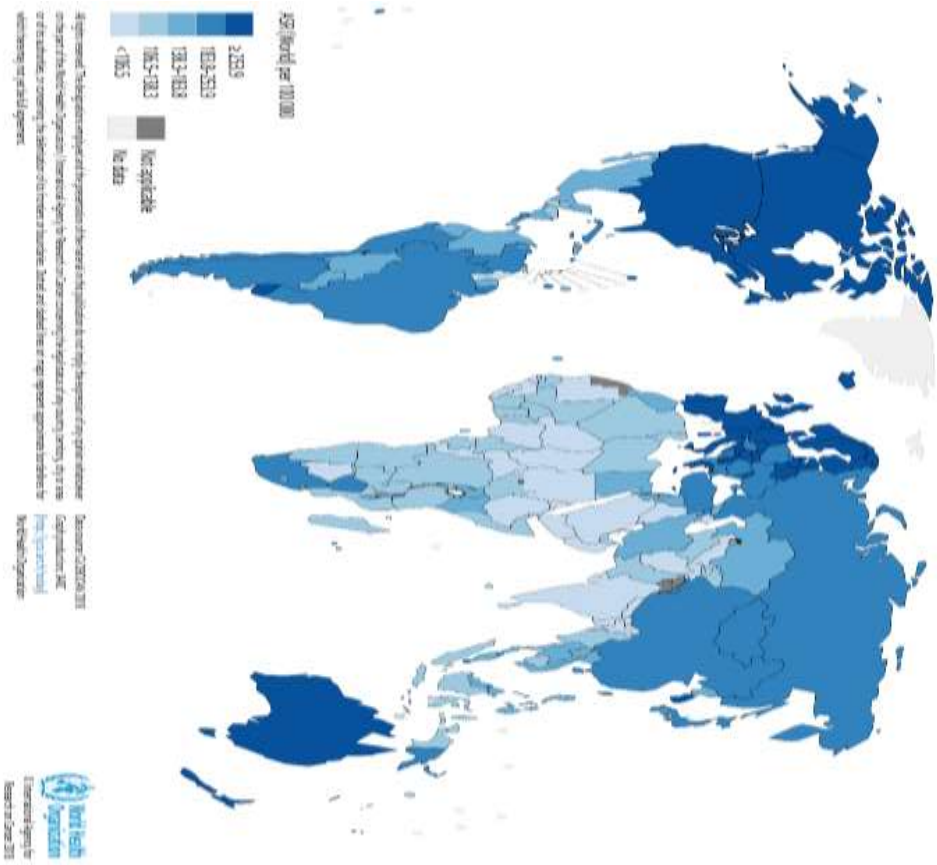

Figure 2: Estimated age-standardized incidence rates (World) in 2018, both sexes all ages

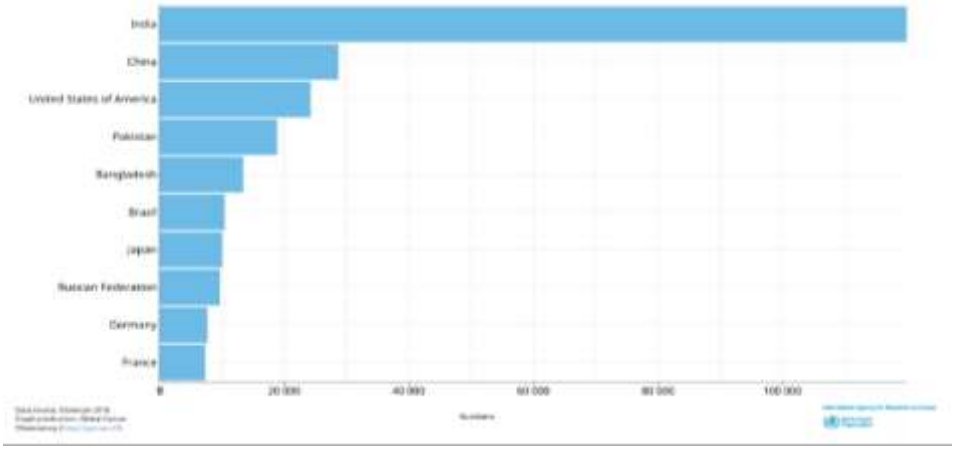

Figure 3: Estimated number of incident oral cancer cases, both sexes, all ages.

REFERENCES

1. Ponder, B.A., *Cancer genetics.* Nature, 2001. **411**(6835): p. 336-341.
2. Lichtenstein, A.V., *On evolutionary origin of cancer.* Cancer Cell International, 2005. **5**(1): p. 5.
3. Leemans, C.R., P.J. Snijders, and R.H. Brakenhoff, *The molecular landscape of head and neck cancer.* Nature Reviews Cancer, 2018. **18**(5): p. 269.
4. Kumar, M., et al., *Oral cancer: Etiology and risk factors: A review.* Journal of cancer research and therapeutics, 2016. **12**(2): p. 458.
5. Rao, S.V.K., et al., *Epidemiology of oral cancer in Asia in the past decade-an update (2000-2012).* Asian Pacific journal of cancer prevention, 2013. **14**(10): p. 5567-5577.
6. Madani, A.H., et al., *Risk assessment of tobacco types and oral cancer.* American Journal of Pharmacology and Toxicology, 2010. **5**(1): p. 9-13.
7. Johnson, N., *Tobacco use and oral cancer: a global perspective.* Journal of dental education, 2001. **65**(4): p. 328-339.
8. Gupta, P.C., P. Murti, and R. Bhonsle, *Epidemiology of cancer by tobacco products and the significance of TSNA*, in *Tobacco-Specific N-Nitrosamines Recent Advances*. 2017, Routledge. p. 183-198.
9. Pemberton, M., *Oral cancer and tobacco: developments in harm reduction.* British dental journal, 2018. **225**(9): p. 822.
10. Benowitz, N.L., J. Hukkanen, and P. Jacob, *Nicotine chemistry, metabolism, kinetics and biomarkers*, in *Nicotine psychopharmacology*. 2009, Springer. p. 29-60.
11. Sanner, T. and T.K. Grimsrud, *Nicotine: carcinogenicity and effects on response to cancer treatment–a review.* Frontiers in oncology, 2015. **5**: p. 196.
12. Winn, D., et al., *The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer.* Oral diseases, 2015. **21**(6): p. 685-693.
13. Asthana, S., et al., *Association of smokeless tobacco use and oral cancer: a systematic global review and meta-analysis.* Nicotine and Tobacco Research, 2019. **21**(9): p. 1162-1171.
14. Cogliano, V.J., et al., *Preventable exposures associated with human cancers.* Journal of the National Cancer Institute, 2011. **103**(24): p. 1827-1839.
15. Ogden, G., *Alcohol and mouth cancer.* British dental journal, 2018. **225**(9): p. 880-883.

16. Conway, D., M. Purkayastha, and I. Chestnutt, *The changing epidemiology of oral cancer: definitions, trends, and risk factors.* British dental journal, 2018. **225**(9): p. 867-873.
17. Hashibe, M., et al., *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.* Journal of the National Cancer Institute, 2007. **99**(10): p. 777-789.
18. Hashibe, M., et al., *Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium.* Cancer Epidemiology and Prevention Biomarkers, 2009. **18**(2): p. 541-550.
19. Gupta, B. and N.W. Johnson, *Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific.* PloS one, 2014. **9**(11).
20. Croucher, R., M. Dahiya, and K.K. Gowda, *Contents and price of vendor assembled paan quid with tobacco in five London localities: a cross-sectional study.* Tobacco control, 2013. **22**(2): p. 141-143.
21. Siddiqi, K., et al., *Smokeless tobacco use by south Asians.* The Lancet Global Health, 2013. **1**(2): p. e71.
22. Petersen, P.E., *Oral cancer prevention and control–the approach of the World Health Organization.* Oral oncology, 2009. **45**(4-5): p. 454-460.
23. Gillison, M.L., et al., *Epidemiology of human papillomavirus–positive head and neck squamous cell carcinoma.* Journal of clinical oncology, 2015. **33**(29): p. 3235.
24. D'Souza, G., et al., *Case–control study of human papillomavirus and oropharyngeal cancer.* New England Journal of Medicine, 2007. **356**(19): p. 1944-1956.
25. Heck, J.E., et al., *Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium.* International journal of epidemiology, 2010. **39**(1): p. 166-181.
26. Mehanna, H., et al., *Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region.* Head & neck, 2013. **35**(5): p. 747-755.
27. Anantharaman, D., et al., *Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer.* International journal of cancer, 2017. **140**(9): p. 1968-1975.
28. Smith, J.S., et al., *Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update.* International journal of cancer, 2007. **121**(3): p. 621-632.
29. Negri, E., et al., *Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium.* International journal of cancer, 2009. **124**(2): p. 394-401.
30. Lingen, M., et al., *Genetics/epigenetics of oral premalignancy: current status and future research.* Oral diseases, 2011. **17**: p. 7-22.
31. Kalavrezos, N. and C. Scully, *Mouth cancer for clinicians part 5: risk factors (other).* Dental update, 2015. **42**(8): p. 766-778.
32. Conway, D.I., et al., *Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries.* International journal of cancer, 2015. **136**(5): p. 1125-1139.
33. Hashim, D., et al., *The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium.* Annals of Oncology, 2016. **27**(8): p. 1619-1625.

34. Gandini, S., et al., *Mouthwash and oral cancer risk quantitative meta-analysis of epidemiologic studies.* Annals of Agricultural and Environmental Medicine, 2012. **19**(2).
35. De Vito, R., et al., *Shared and study-specific dietary patterns and head and neck cancer risk in an international consortium.* Epidemiology (Cambridge, Mass.), 2019. **30**(1): p. 93.
36. Arnold, M., et al., *Obesity and cancer: an update of the global impact.* Cancer epidemiology, 2016. **41**: p. 8-15.
37. Gaudet, M.M., et al., *Body mass index and risk of head and neck cancer in a pooled analysis of case–control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium.* International journal of epidemiology, 2010. **39**(4): p. 1091-1102.
38. Toporcov, T.N., et al., *Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium.* International journal of epidemiology, 2015. **44**(1): p. 169-185.
39. Shield, K.D., et al., *The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012.* CA: a cancer journal for clinicians, 2017. **67**(1): p. 51-64.
40. Simard, E.P., L.A. Torre, and A. Jemal, *International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site.* Oral oncology, 2014. **50**(5): p. 387-403.
41. Chaturvedi, A.K., et al., *Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers.* Journal of clinical oncology, 2013. **31**(36): p. 4550.
42. Hashibe, M. and E.M. Sturgis, *Epidemiology of oral-cavity and oropharyngeal carcinomas: controlling a tobacco epidemic while a human papillomavirus epidemic emerges.* Otolaryngologic Clinics of North America, 2013. **46**(4): p. 507-520.
43. Johnson, N.W., et al., *Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions.* Advances in dental research, 2011. **23**(2): p. 237-246.
44. Johnson, N.W., et al., *Epidemiology and site-specific risk factors for oral cancer*, in *Contemporary Oral Oncology*. 2017, Springer. p. 103-153.
45. Gupta, N., et al., *Changing Trends in oral cancer-a global scenario.* Nepal journal of epidemiology, 2016. **6**(4): p. 613.
46. Warnakulasuriya, S., *Global epidemiology of oral and oropharyngeal cancer.* Oral oncology, 2009. **45**(4-5): p. 309-316.
47. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012.* European journal of cancer, 2013. **49**(6): p. 1374-1403.
48. Neville, B.W. and T.A. Day, *Oral cancer and precancerous lesions.* CA: a cancer journal for clinicians, 2002. **52**(4): p. 195-215.