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Epidemiology and Aetiopathogenesis of Oral Malignancy: Current Trends

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Abstract

Malignancy of oropharynx and oral cavity has seen a rising trend in the past 2 decades. With increasing globalisation, sedentary lifestyle and poor oral hygienichabits, cancers of various parts of oral cavity have become more and more common. Squamous cell carcinoma is the commonest head and neck malignancyand also most frequently seen in the oropharynx. It is associated with tobacco and alcohol consumption; owing to the synergistic action of these two carcinogens. The last 20 years have also seen a rise in HPV associated cancers. In this chapter, we will discuss the current epidemiological trends and aetiopathogenesis in development of oral malignancies in various parts of the world.

Keywords

Epidemiology; Oral Cavity; Oropharynx; Worldwide; Cancer; Malignancy

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Introduction

Oral malignancy is a broad term which includes all the carcinomas that can arise in oral cavity and oropharynx (Figure 1). These are ranked as 6th leading cancers in the world, according to the incidence, and histologically, 90% of these are SCCs i.e. squamous cell carcinoma [1]. If identified in the later stages, the 5- year survival rate is less than 50%, especially in women who have a much favourable outcome [2]. Prognosis of such patients dependent on lymph node metastasis, age of the patient and size of the primary tumor size and it's location [3]. Risk factors associated with development of carcinoma include alcohol, tobacco, and betel nut consumption, occurrence of premalignant conditions like erythroplakia, leukoplakia, poor oral hygiene, exposure to ultra-violet radiation, Human Papilloma Virus (HPV) most importantly HPV 16 and 18 and Epstein Barr Virus (EBV)[4]. Non-squamous malignancies have also been reported but they are less commonly seen, and mostly involve the minor salivary glands.

Histopathological types of Malignancy

The following flowchart (Figure 1) gives a brief outline of the histopathological types ofcancers seen in oropharynx and oral cavity.

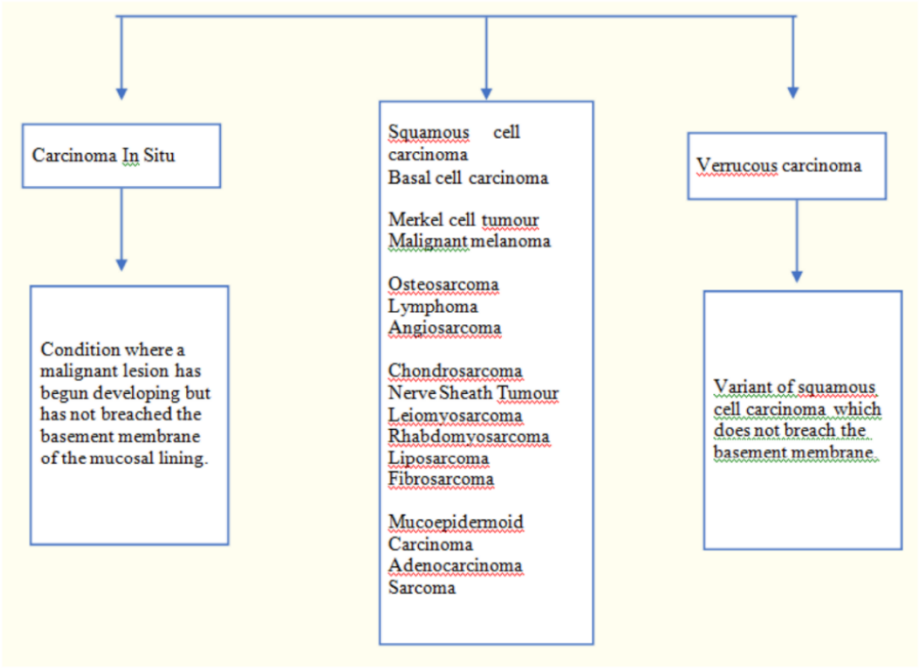

Figure 1: Flowchart showing various histopathological types of cancer in oropharynx.

Aetiopathogenesis of Oral Cancer

The following flowchart (Figure 2) gives an outline of the various causal agents of oralmalignancy [5]. Carcinogenesis in the oral cavity is similar to any other malignancy in the fact that it is a progressive disease

and the normal epithelial mucosa passes through various stages beginning from dysplasia to metaplasia and ultimately transforming into anaplastic changes and furthermore malignancy. Numerous causal agents for oral carcinoma (OC) have been described. Chemicalfactors namely alcohol, tobacco [6] oro-dental factors [7], infections like HPV [8],HSV [9] syphilis, immunocompromised conditions like HIV/AIDS [10], genetic mutations [11,12] dietary deficiencies [13] and chronic candidiasis have been known to be associated with this condition.

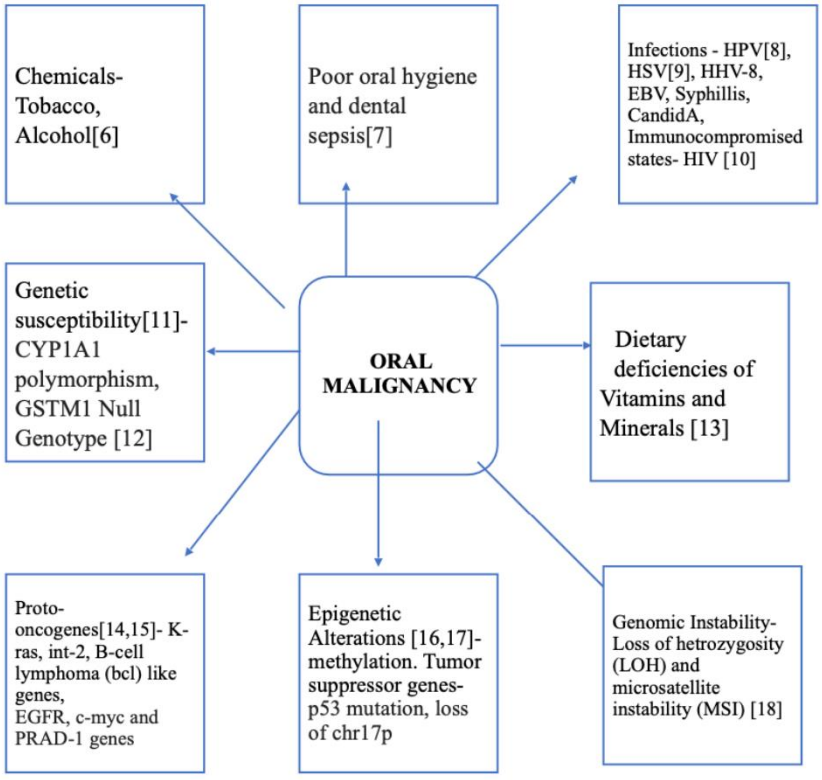

Figure 2: Flowchart showing various risk factors of oropharyngeal cancer.(Reproduced with permission from IARC)21.

Tobacco smoke can be used in various forms like pipe, bidi, cigarrettes, cigars, etc. Chillum which is a clay pipe used to keep burning tobacco and hookah, are common forms of smoking in some Asian countries including India [6]. In the state of Mizoram, which is located in the north-eastern part of India, tobacco smoke is consumed as “smoke on the water”, i.e. by dissolving in water. Some degree of controversy is there regarding the synergistic carcinogenic effect of simultaneous use of tobacco and alcohol, which has been observed in numerous epidemiological studies [19]. Alcohol can have an additive effect and evidence suggests that it may alter the metabolism of cells of oral mucosa and also facilitates the entry of carcinogens into the exposed cells.

An emerging area of latest research are the oncogenic viruses and their effect on causation of carcinoma [14,15]. Viruses have the ability to capture the host cells and can get integrated in the nucleus giving rise to oncogenic mutations and uncontrolled proliferation by modification of DNA. HSV [5] and HPV [6] have been established as the causal agents of OC. The risk of pharyngeal and oral cavity carcinoma is two-times

higher in patients affected by HIV i.e. human immunodeficiency virus [10], suggesting a strong connection between oral squamous cell carcinoma (OSCC) and HIV. Cytomegalovirus (CMV), Human Herpes Virus (HHV-8) and Epstein Barr Virus (EBV) have also been implicated as risk factors of OSCC in numerous studies [13,14].

Recent clinical research has also reported that candida infection in nodular leukoplakia has a tendency for high rate of metaplasia and dysplasia. It has also been observed that chick embryo epithelium, when affected with candidiasis shows raised proliferation [20]. Carcinogenesis in the oral cavity is similar to any other malignancy in the fact that it is a progressive disease and the normal epithelial mucosa passes through various stages beginning from dysplasia to metaplasia and ultimately transforming into anaplastic changes and furthermore malignancy. The most common type of cancer seen in the oral cavity and oropharynx is the squamous cell carcinoma, although other forms are also seen. With the advent of proteomics and genetic research, the molecular pathogenesis of OC has come to light, which aims to focus on the changes in porto-oncogenes or tutor suppressor genes. Studies re ongoing to identify the role of epigenetic modifications and genomic instability in order to create a eugenic expression profile in oral carcinogenesis [16,17]. Though, some significant leads have been achieved, a further understanding of the molecular pathology of Oral Carcinoma along with its association with various causal agents will require more decades of extensive research.

Worldwide Statistics

Asia

Incidence and Prevalence

South Asia

Prevalence in India ranges from 0.17% to 9.85% across all the states. A statistically significant fall in ASIR (Age-Standardized Incidence Rate) was seen in Mumbai among females, i.e. from 6.90 in 1995 to 6.10 in 2009. Over the sametime period, the incidence of males was seen to increase from 1.90 to 3.40 [22].

East Asia

The ASIR of Hong Kong (1.49), Korea (1.48, 3.43) and China (2.06, 1.34) averaged less than 2.0 in the last decade. Japan had the highest rate of incidence of 3.80 in 2014. The incidence among Hong Kong males fell from 2.26 in 1983 to 1.49 in 2014. [22].

West Asia

Among the West Asian countries, only UAE, Iran and Iraq and have reported prevalence and incidence rates, out of which UAE had the maximum prevalence in Asia, i.e.14.82% [22].

Southeast Asia (SEA)

The countries having a high ASIR are Thailand (4.00) , Myanmar (6.20), and Brunei (6.00), whereas Indonesia has the lowest incidence at 2.30 [22].

Sites and Subsites-

The tongue is the most frequently affected site, followed by the mucosa of buccal cavity. Pakistan and Taiwan have the most number of cancer cases in the buccal mucosa, but other countries have also reported conflicting findings. Studies conducted in Thailand have demonstrated malignancy either in the gingiva or tongue, whereas in Iran it is either the lips or tongue, as the predominantly affected sites. Among the studies conducted in India, mandibular alveolus, tongue and buccal mucosa, have been

described as the main sites for occurrence of OC [22], due to the habit of betel nut chewing and keeping it overnight in the gingivo-labial sulci.

Age and Gender Predisposition

The average age of affected patients is most commonly the late fifties. Highest mean age (64.14) is seen in Hong Kong Hong Kong (64.14), in contrast Qatar (46.93) has the lowest. A wide range is seen in Thailand i.e. from 3 to 101 years old [8]. It is seen that oral cancer affects males, higher than females among all age groups (Figure 2). Majority of the countries have a Male: Female ratio within Figure 2: Depicting number of new cases and mortality in both sexes in all ages in 2020. (Reproduced with permission from IARC) 21 0.00- 3.00; few fall within 3.00-5.00, and many countries above that. Least gender ratio is seen in Laos (0.53) and Taiwan has the highest (20.09) [22].

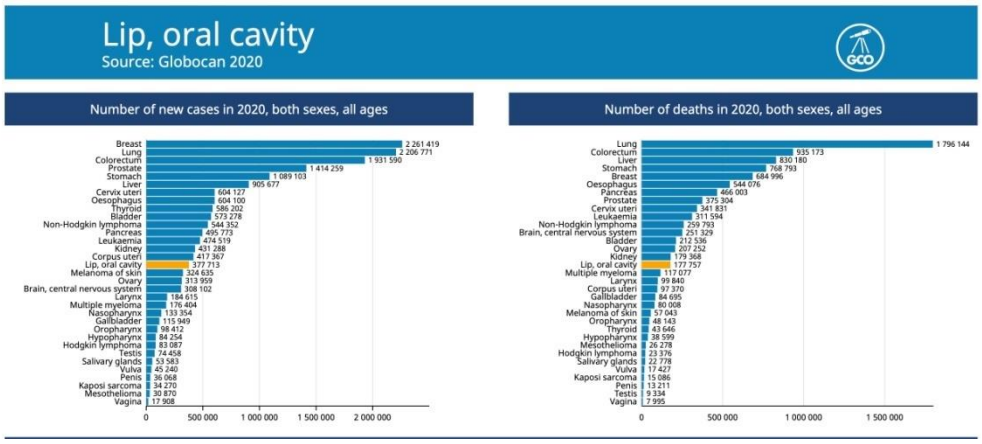

Figure 3: Depicting number of new cases and mortality in both sexes in all ages in 2020. (Reproduced with permission from IARC)21.

North America

USA

Incidence and Prevalence

It is estimated that in the year 2022, around 54,000 new cases of oropharygeal/ oral malignancy and 11,230 deaths from the same will be seen, as reported by TheAmerican Cancer Society [23]. The mean rate of new cases of OC has risen slightlyover the previous 2 decades (Figure 3). But in the same duration, it was reported that HPV Associated cancers [24] have increased, and they act differently than non-HPV malignancies.

Sites and Subsites

Most common sites affected in the United States are tongue, tonsils, floor of mouth, gums, and a small proportion is seen in the minor salivary glands and lips. Alcohol, tobacco and smoking are major risk

factors contributing to the incidence of oral and oropharyngeal cancers in the United States, along with HPV infection [24] in papilloma positive cancers.

Age and Gender Predisposition

The mean age of maximum patients diagnosed with OC is 63 years, but it might also occur among the younger patients. An estimated 20% cases of oral malignancy (1 out of 5) develop in patients younger than 55 years [25]. A similar trend is seen here as well, that men are more commonly aflicted than women, and they're seen more in White population. The lifetime overall risk of development of oropharyngeal and oral cavity cancer is about 1 in 140 (0.71%) for women and 1 in 60 (1.7%) for men. The average death rate for these cancers has fallen over the past 30 years, due to the advancements in treatment regimens .

Canada

Incidence and Prevalence

As per the 2019 Canadian Cancer Statistics report, approximately 7,500 Canadians will be suffering from OC by the year 2022, out of which 2,100 (Figure 4).

Sites and Subsites

In Canada, oropharyngeal and oral malignancy is thrice as common than cervical cancer and more frequently seen than liver cancer [26].

Cancer incidence and mortality statistics worldwide and by region

	Incidence						Mortality					
	Both sexes		Males		Females		Both sexes		Males		Females	
	New cases	Cum. risk 0-74 (%)	New cases	Cum. risk 0-74 (%)	New cases	Cum. risk 0-74 (%)	Deaths	Cum. risk 0-74 (%)	Deaths	Cum. risk 0-74 (%)	Deaths	Cum. risk 0-74 (%)
Eastern Africa	4 653	0.22	2 690	0.28	1 963	0.18	2 980	0.16	1 716	0.20	1 264	0.12
Middle Africa	1 431	0.18	879	0.23	552	0.13	904	0.12	552	0.16	352	0.09
Northern Africa	3 216	0.16	1 727	0.19	1 489	0.14	1 466	0.07	739	0.08	727	0.06
Southern Africa	2 132	0.45	1 305	0.66	827	0.28	914	0.20	596	0.33	318	0.10
Western Africa	2 854	0.16	1 573	0.17	1 281	0.14	1 824	0.11	1 003	0.12	821	0.10
Caribbean	1 679	0.33	1 193	0.53	486	0.16	668	0.12	482	0.20	186	0.04
Central America	2 018	0.12	886	0.12	1 132	0.12	853	0.05	446	0.06	407	0.04
South America	14 191	0.29	9 636	0.46	4 555	0.14	6 027	0.12	4 252	0.21	1 775	0.05
Northern America	27 469	0.51	18 513	0.73	8 956	0.29	4 985	0.08	3 224	0.11	1 761	0.04
Eastern Asia	51 158	0.21	33 658	0.29	17 500	0.13	21 933	0.08	14 083	0.11	7 850	0.05
South-Eastern Asia	18 381	0.29	11 297	0.38	7 084	0.21	9 925	0.15	6 409	0.21	3 516	0.09
South-Central Asia	174 448	1.01	130 725	1.48	43 723	0.53	98 015	0.59	72 311	0.84	25 704	0.33
Western Asia	4 373	0.20	2 716	0.26	1 657	0.14	1 737	0.08	958	0.09	779	0.06
Central and Eastern Europe	26 083	0.61	19 884	1.12	6 199	0.21	12 490	0.29	9 761	0.56	2 729	0.09
Western Europe	17 770	0.55	11 127	0.76	6 643	0.36	5 133	0.14	3 419	0.21	1 714	0.07
Southern Europe	12 387	0.42	7 926	0.61	4 461	0.23	4 234	0.13	2 751	0.20	1 483	0.06
Northern Europe	9 039	0.54	5 582	0.72	3 457	0.36	2 718	0.14	1 714	0.20	1 004	0.08
Australia and New Zealand	3 096	0.70	2 070	1.01	1 026	0.41	469	0.09	281	0.13	188	0.05
Melanesia	1 299	2.05	796	2.82	503	1.35	468	0.82	313	1.19	155	0.48
Polynesia	20	0.32	16	0.52	4	0.12	8	0.11	7	0.22	1	0
Micronesia	16	0.36	12	0.64	4	0.12	6	0.16	5	0.34	1	0
Low HDI	10 126	0.22	5 883	0.27	4 243	0.17	6 251	0.15	3 622	0.18	2 629	0.12
Medium HDI	177 018	0.91	132 012	1.35	45 006	0.48	99 662	0.53	73 289	0.77	26 373	0.29
High HDI	72 418	0.21	46 009	0.29	26 409	0.14	34 765	0.10	22 857	0.14	11 908	0.06
Very high HDI	118 036	0.50	80 219	0.76	37 817	0.26	37 048	0.14	25 230	0.23	11 818	0.06
World	377 713	0.46	264 211	0.68	113 502	0.26	177 757	0.22	125 022	0.32	52 735	0.12

Figure 4: Depicting cancer incidence and mortality worldwide and by region. (Reproduced with permission from IARC)21.

Age and Gender Predisposition

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The 2019 statistics report suggests that out of the total cases of oropharyngeal and oral malignancy, 1600 were women and 3700 were men, of which 1480 died (including 430 women and1050 men), suggesting that women are less affected as compared to men [27].

Latin America

Incidence and Prevalence

Latin America is considered a region with high prevalence and incidence of oral and oropharyngeal cancer [28]. There's going to be an estimated 22.4% rise in the percentage of new cases of OC between the years 2018 and 2025; the same goes for mortality rates [29]. Countries with the maximum age standardised incidence rates are Puerta Rico, Brazil, Uruguay and Cuba [29]. Brazil and Cuba also lead the mortality rates in this region due to oral malignancy. The disease burden is expected to rise by 7% in South and Central America i.e. 37,909 deathsand 72,985 new cases.

Sites and Subsites

Latest studies have shown that HPV-positive cancers comprise approximately 25% of all the head and neck malignancies. The prevalence is more in larynx (24.0%), oral cavity (23.5%) and oropharyngeal cancer (35.6%). The most common genotype found is HPV16, which is a high-risk subtype [28].

Age and Gender Predisposition

Brazilian males have the highest risk worldwide for OC, following that of India and France. [29]. It has been found that Cuban and Brazilian males have a high mortality from these malignancies than those of males in Canada and the UnitedStates. [30]. Although a fall in death rates has been observed among Chilean andArgentinean men, mortality rates in Cuba due to these malignancies are still rising in both in the sexes [30]. These findings are particularly concerning as incidence estimates for most South and Central American countries are still lacking (Figure 5).

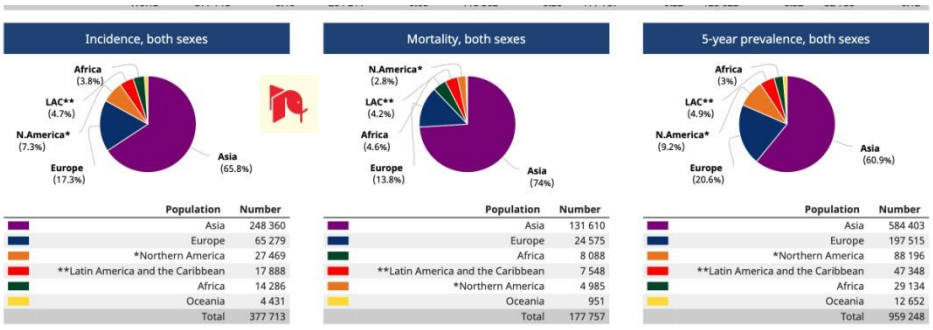

Figure 5: Pie charts showing incidence, mortality and 5-year prevalence in both sexes. (Reproduced with permission from IARC).

Africa

Incidence and Prevalence

There's a sparcity in the scientific literature regarding data from Africa, due to lack of infrastructure and less number of cancer registries [31]. Hence, it has become quite tough to extrapolate the disease pattern in the African countries [32]. Many patients present to the clinician in late stages of the diseasemost important reason being higher number of HIV-Positive cases in some of the Sub-Saharan countries, amounting to the high mortality rates in this region [33].

Sites and Subsites

Among head and neck malignancies, the most commonly affected site is the oral cavity. Further research needs to be conducted to accurately identify which subsite is most commonly affected [34].

Age and Gender Predisposition

The highest and lowest peak incidence of tumors is seen in the fourth (18.3%) and second (5.9%) decades, respectively, according to the GLOBACON 2020 (Figure 2). A slight female predominance (50.1%) was seen over males (49.9%) inNigeria, with a ratio of 1.01:1[35] (Figure 6,7).

permission from IARC)21

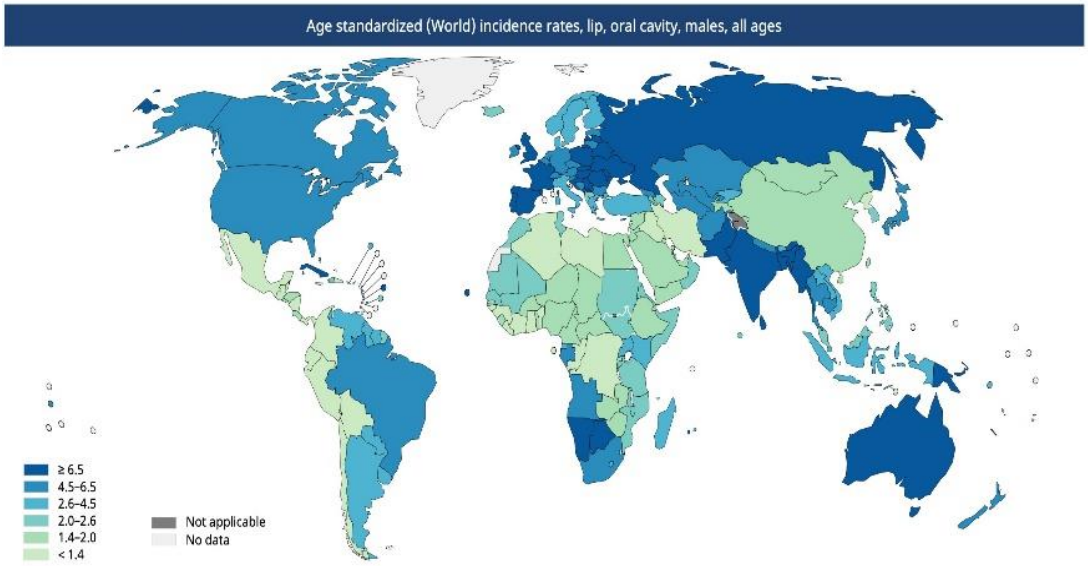

Figure 6: World map showing ASIR in males, in all ages. (Reproduced with permission from IARC)21.

Europe

Incidence and Prevalence

An estimated 35,000 people in Europe suffered deaths as a result of oral cavity,lips and other pharyngeal carcinomas in the year 2019, research shows [36]. There's been a 45% rise in the incident cases of lip, oral cavity, nasopharynx andother cancers (LOCP) [37] from the year 1990 to 2019; and, the ASIR (Age standardised incidence rate) increased by 3.1%, whereas there has been a fall in the age standardised mortality rates by 16% [38].

Sites and Subsites

The most commonly affected subsite for oral malignancy observed in Europe is the lip, and for HPV-associated cancers is the tonsil, and the oropharynx [39].

Age and Gender Predisposition

There's a vast gender variation among the European countries and predispositionof oral malignancy due to the varying eating and drinking habits of the people as well as depending on the status of the healthcare system.

France had the highest number of new male LOCP cases among all age groups in1990 [Figure 5]. However, in the year 2019 there was a change in the trend, i.e, LOCP rate for men ranked 3rd for 70+ year olds, 4th for 50–69 year olds and 8th for 15–49 year olds, pointing towards a probable effect of cohort. A falling LOCPfemale trend was also observed in the same region. Improved universal health care and oral health are possible reasons for such age-gender variations. [40]. The maximum LOCP rates for women in Europe were seen in Hungary [41] during these 3 decades, likely reason being excessive consumption of alcohol andtobacco, as well as a poor structure of the Hungarian health industry. On the other hand, Cyprus has shown a constant pattern across all the age groups. For example, the new cases of LOCP were the least in this country among men aged 50–59 in 1990 and 2019. Latest research has shown that Cypriots have a high lifeexpectancy in the EU (European Union), and this can be credited to general goodhealth status [42]. Less alcohol intake and healthier dietary habits suggest a much better status of the general population.

Australia

Incidence and Prevalence

Just like other developed countries, the rates of oral and oropharyngeal malignancy have risen in Australia as well since the past 2-3 decades [43,44]. Evidence suggests that a major risk factor for cancers in this region is the HPV (human papillomavirus) specifically the 16 and 18 type, attributing to the high prevalence of oral sexual (OS) activity and early age-onset of OS in this region.

Sites and Subsites

Among all the head and neck subsides, oropharyngeal cancers are more commonly reported in Australian population, attributed to the high prevalence ofHPV infection, as a result of oral sexual activity [45].

Age and Gender Predisposition

During the years 1982-2017, there was a normal distribution of OPC (oropharyngeal cancer), with peak age at 55-69 years, due to the time taken for viral proliferation and activation [46]. Early age onset of oral sexual activity, previous experiences with oral sex and more number of oral sexual partners (OSP) are key factors in persistence of thisinfection in the oropharyngeal mucosa and oral cavity [47] which in turn, raisesthe risk of HPV-associated oropharyngeal carcinoma (OPC). There has been a further ascension of

OPC cases from the year 2008 to 2017, significantly in males, and less in females (Figure 6). This was observed in spite of a reduced alcohol and tobacco intake [45].

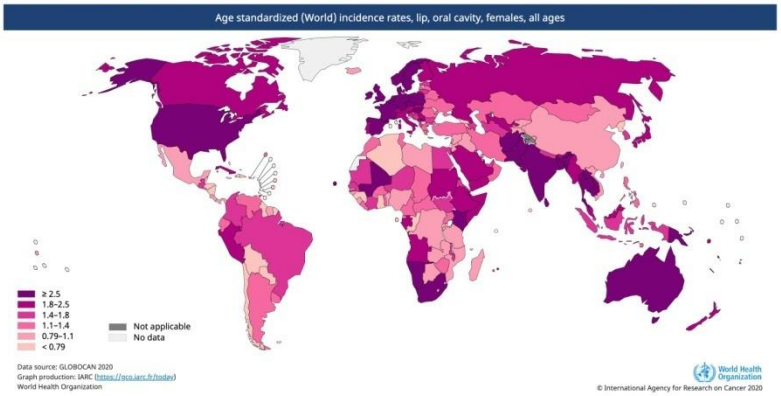

Figure 7: Worldmap showing ASIR in Females, in all ages. (Reproduced with permission from IARC)21

Conclusion

OC causes significant damage in swallowing, chewing and speech, and hasbecome quite prevalent all over the world, with varying trends in differentregions (Figure 8).

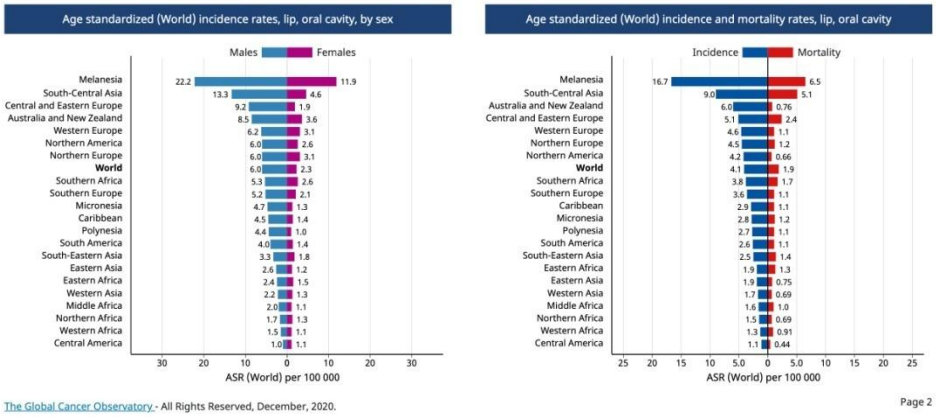

Figure 8: ASIR worldwide incidence and mortality rates (Reduced with permission from IAR)21

With advances in technology, there is now enough understanding of risk factors to prevent 1/3rd of all carcinomas worldwide and there are sufficient resources to facilitate early detection and timely treatment of those cases [48]. It is extremely important to promptly identify cancers in the first instance, just by examination, so that the there's minimum time delay between diagnosis and initiation of treatment. The

clinician should also take this opportunity to educate the patient about the risks of the disease and the lifestyle modification necessary to lower theincidence of the disease. It is extremely important to keep researching about the specific biomarkers so that there's continuous progress in this field, so as to enable better and early detection is enabled.

Conflict of Interest

There are no conflict of interest to disclose.

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