EPIDEMIOLOGY OF ORAL AND PHARYNGEAL CANCER

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ABSTRACT
Oral cancer is a public health problem, representing the sixth most common malignant neoplasm. The annual estimated incidence is approximately 300,000 oral cancers; two thirds of these cases occur in developing countries. The incidence of oral cancers among men is highest in northern India, a few areas of central and eastern Europe and Latin America. Among women, the incidence is high in south and southeast Asia. In Asian countries the high incidence rates were reported from developing nations like India, Pakistan, Bangladesh, Taiwan and Sri Lanka. While an increasing trend has been observed in Pakistan, Taiwan and Thailand, a decreasing trend is seen in Philippines and Sri Lanka. Information on survival of patients with oral cancers was very restricted. Tongue cancers displayed the worst survival rates in Latin America, India and Yemen. Some countries shares specific risk factors namely heavy tobacco smoking and alcohol consumption and high intake of charcoal-grilled red meat and mate. In addition, other specific risk factors are viral infection (HPV), poor oral hygiene, chewing of betel-quid, gutka, Zarda, Kharra, snuff and Qat. Urgent public health measures are needed to reduce the incidence and mortality of oral cancer.

KEYWORDS: Epidemiology, Oral cancer, Risk factors.

1. INTRODUCTION
Cancer of the oral cavity which may occurs in any part of the mouth or throat. Is spreads locally involving perioral structures and metastasises to local regional lymph nodes. Is curable if discovered early. Oral cancer usually includes cancer of the lip, tongue, salivary glands, and other sites in the mouth; while pharyngeal cancer includes cancers of the nasopharynx, oropharynx and hypopharynx (Warnakulasuriya, 2009). Oral cancer spreads locally involving perioral structures and metastasises to local regional lymph nodes. This chronic disease is a public health problem affecting quality of life in both developing as well as developed countries.

The annual estimated incidence is approximately 300,000 oral cancers; The developing nations have been reported to have more incidence of oral cancer when compared to the developed nations (Cancela et al., 2010) of which India, South America and Oceania are mostly affected (Warnakulasuriya, 2009). The most common type of oral cancer is squamous cell carcinoma causing 90% of oral cancer (Ariyoshi et al 2008; Kruaysawat et al 2010) which arise from preexisting potentially malignant lesions or more often from normal appearing epithelium. Oral cancer is the most common leading cause of death across the globe, and the chronic public health problem both in the developing as well as developed world. Men are affected 2 to 3 time as often as women largely due to higher use of alcohol and tobacco and poor oral hygiene. (Gupta et al 2003). Although the disease has been reported in various age group but it occurs frequently in patients over the age of 60 years (Najjar and Gatson 1980).

2. Global Incidence
Oral and pharyngeal cancers are significant components of the global burden of cancer. The worldwide cases of oral cancer in 2012 in both sexes were about 300,000 (2.1% of the total cancers) and approximately 145,000 cases were fatal (Ferlay et al 2010). Two-thirds of oral and pharyngeal cancers (excluding nasopharynx) occur in developing countries. (Warnakulasuriya et al 2009) Figure. 1 illustrates the significant geographical variation that exists for the incidence of oral cancer. It is very high incidence rates reported from developing countries situated in South-Central and South East regions like Pakistan, India, Bangladesh, Sri Lanka and Taiwan. In India more than 35% of total burden cancers are attributed to oral cancers (Parkin et al 2005). Oral cancers are the most common cancer in males in high-risk areas such as Sri Lanka, India, Pakistan, and Bangladesh and accounts for up to 25% of all new cancers. The principal causes of oral cancer are tobacco (smoked or chewed) and betel quid. Buccal cancer is common in Asia due to its association with betel quid and tobacco chewing; 40% of oral cancers in Sri Lanka
are buccal carcinomas. (Parkin et al 2005). The lifetime risk of developing oral cancer in Europeans is estimated at 1.85% for men and 0.37% for women. The incidence rates are higher in western Europe compared with Northern or southern Europe. Highest mortality rates, however, are reported from eastern Europe.

Overall in the EU, oral and pharyngeal cancer occupies the 7th position (Boyle et al 2005). In United States about 34360 cases of oral cancer and pharyngeal cancer were reported. The incidence rate of oral cancer is generally expressed for 100000 population incidence in Five Continents, utilised incidence rates for a defined period. (Ferlay et al 2008). The Age standardized incidence rate (ASIR) is more than 20 per 100,000 populations in India and more than 10 per 100,000 populations in Pakistan, India, Taiwan, Sri Lanka and Bangladesh, and ARIR less than 6/100,000 in China, Vietnam, Japan, Singapore and Philippines and less than 2 per 100,000 populations in Middle East (Ferlay et al 2010, Conway et al 2008).

Figure 1. Countries with high incidence and mortality from oral cancer

Within the EU countries the highest male incidence rates are found in France and Hungary and the lowest rates are found in Greece and Cyprus. Black R. J et.al report the rate for oral cancer in men in France was almost seven times greater than that for men in Greece. In contrast to the divergent patterns observed among men, incidence trends for OPC and OCC were statistically similar in a majority of countries among women. With the exception of Denmark, in all other countries with significant increases in OPC incidence among women (France, the Netherlands, Slovakia, Switzerland and United Kingdom. The prevalence of oral cancer is high in Asian countries especially Southeast Asia (Reichart and Way, 2006). Asians have distinct cultural practices such as betel-quid chewing as well as, varying patterns of use of tobacco and alcohol which are important risk factors that predispose to cancer of oral cavity.

Figure 2: Incidence of oral cavity among men expressed by level of age-standardized rate in countries of the world (Source: GLOBOCAN 2002 international agency for Research on Cancer http://www.depdb.iarc.fr/globocan2002.htm)
3. Trends
Oral cancer is a heterogeneous group of cancer arising from different parts of the oral cavity, with different predisposing factors, prevalence and treatment outcome.

Among men, significant increases in OPC incidence during 1983 to 2002 were observed predominantly in economically developed countries; Japan, Australia, Denmark, the Netherlands, Slovakia, United Kingdom, Canada, United States and Brazil. (Anil K et al 2013).

Ahmedin Jema et al 2011 report Age-Standardized Oral Cavity Cancer Incidence Rates by Sex and World Area was the highest oral cavity cancer rates are found in Melanesia, South-Central Asia and Central and Eastern Europe and the lowest in Africa, Central America and Eastern Asia for both males and females.

Oral cavity cancer mortality rates among males decreased significantly in most countries, including those of Europe and Asia, over the past decades.(Mayne et al 2006). But rates continued to increase in several Eastern European countries, including Hungary and Slovakia (Garavello et al 2010). The increase in females in most...
European countries largely reflects the ongoing tobacco epidemic.

4. Age and gender
The incidence of oral cancer is low in people below the age of 45 (Ferlay 2001). The incidence of oral cancer increases with age, though the pattern differs in different countries and with different risk factors. Like most cancers, the incidence of oral cancers rises with age. Patients over 60 years of age are at the greatest risk; however, the incidence of oral cancer has increased in patients under 40 years of age, perhaps because of changing risk factors. About 6% of oral cancers occur among persons under 40 years of age. Males had higher prevalence of oral cancer in all the age groups when compared to females.

In all countries men are affected almost twice as often as women, probably due to their higher indulgence in risk factors such as alcohol and tobacco consumption, for intraoral cancer and sunlight for lip cancer (Mathew et al 2001). In 1996 – 2002, 11.19% males and 10.04% females were less than 45 years of age while in 1988 – 1991, 15.6% were males and 14.1% were females (figures calculated from the 1988-1991 study) (Hille et al., 1996).

5. Oral cavity sites
There is a strong association between the site of cancer and the site where the quid is placed regularly. Pooling of carcinogens in saliva give rise to cancers in the floor of the mouth and ventral and lateral tongue.

The oral cavity sites depend on the type of predominant risk factors. Most type of tongue cancers begins in the upper layer of the tongue and is termed as squamous cell carcinomas. Smoking is more strongly associated with soft palate and larynx cancers and alcohol with floor of the mouth and tongue lesions (Boffetta 1992). Lip cancer is most common in fair skinned races, particularly in rural areas and in men who work out of doors. Use of alcohol and tobacco chewing are considered to be the two major tongue cancer causes. Oral tobacco products (snuff or chewing tobacco khat and Zarda) are linked with cancers of the cheek, gums and inner surface of the lips. Lip cancer is three times more common in men than women which may be an effect of occupation, smoking and sun-exposure (Perea-Milla López E et al 2003). HPV-related oropharyngeal cancer in the tonsils and the base of the tongue has become more common in recent years. (Campisi et al 2006). Chronic irritation to the lining of the mouth from poorly fitting or defective complete dentures may be a risk factor for oral cavity and gum (Rosenquist et al 2005).

6. Risk Factors
Tobacco, betel quid and alcohol are strong risk factors for both oral cavity cancers (OCC) and oropharyngeal cancers (OPC) (Hashibe 2007). In contrast, the association of human papillomavirus (HPV) is heterogeneous; HPV is an established cause of OPC (including the tonsil, base of the tongue and other parts of the pharynx) whereas its etiologic role in OCC is unclear (Souza et al 2007).

Alcohol consumption is also a recognized risk factor for oral cancer, particularly when combined with tobacco usage, where it has an additive effect. Rodriguez et al found that oral cancer was associated with alcohol drinking in never smokers and with tobacco smoking in moderate drinkers. They also suggested that heavy consumption of both alcohol and tobacco produced almost 48-fold increased risk in young people (Rodriguez et al 2004). Many studies have confirmed that there is a synergic effect of cigarette smoking, alcoholic consumption and betel quid chewing in carcinogenesis of oral cavity mucosa (Castellsague et al 2004, Wen et al 2010).

6.1 Quid chewing
Quid chewing is an ancient ethnic practice in Southeast Asian countries. Betel quid is chewed owing to its medicinal properties (Raghavan et al. 1958) and as a symbol of social life. The habit of betel quid chewing is widespread and its use has been documented from the East African coast to Eastern Melanesia and throughout India and South East Asia. The belief that betel quid chewing originated in an area of West Malaysia. Betel chewing probably spread to Southern India in a period of trade and early missionary activity following the Indian colonization of the Malay area and South East Asia. In India, tobacco is frequently added to the quid as shredded sun-dried tobacco leaves or stems, together with catechu (a resin from the Acacia catechu or Acacia suma) and a variety of spices such as, nutmeg, camphor, cloves, cardamon, sandalwood, mace, peppermint and an extract of the flower of Pandanus orordatissimum. Quid in India and Pakistan is called ‘Paan’. The usual constituents of paan are betel leaf (Piper betel), areca nut (Areca catechu) also known as betel nut and lime (calcium hydroxide). Additional use of tobacco and other spices are dependent on individual’s choice (Mack, 2001). Quid chewing has been found to be an independent risk factor for oral cancer. Chewers of betel quid with or without tobacco often develop clinically visible withish (Leukoplakia) are reddish (Erythroplakia) lesions and /or stiffening of the oral mucosa and oral submucous fibrosis. The malignant transformation of non homogenous lesions involving erythroplakia and nodular leukoplakia is particularly high, reportedly ranging from 9 to 37% (Lee JJ 2006). The causal link between chewing quid without tobacco and carcinogenesis has been recognized (Merchant et al., 2000). Areca nut used in betel quid is known to cause oral cancer due to the presence of arecoline specific nitrosamines that are carcinogenic (Warnakulasuriya et al., 2002; Muttagi et al., 2012; Shah et al., 2012). Lime, a constituent of quid, acts as a tumour promoter by hydrolysing alkaloids present in the areca nut to cytotoxic and mutagenic compounds (Shah et al., 2012).
Chewing of tobacco with BQ results in high exposure to carcinogenic tobacco-specific nitrosamines (TSNAs), to ~1000 mg/day (Nair et al. 1999). The carcinogenic TSNAs N’-nitrosornicotine (NNN), 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N’-nitrosoanabasine (NAB), as well as the volatile nitrosamines N-nitrosodimethylamine and N-nitrosodiethylamine, have been detected in the saliva of chewers of BQ with tobacco (Wenke et al. 1984; Nair et al. 1985; Bhide et al. 1986; Nair et al.1987a). TSNAs undergo metabolic activation by cytochrome P450s and other enzymes. NNK, a major carcinogenic TSN, is activated by either methylene hydroxylation to generate an intermediate that decomposes to a DNA-methylating agent, resulting in the formation of 7-methylguanine, O6-methylguanine, (O6-MeG) and O4-methylthymidine in DNA or via methyl hydroxylation to form bulky pyridylloxobutyl DNA adducts. NNK is also converted metabolically to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, which can also be activated by a-hydroxylation to yield methyl and pyridylhydroxybutyl adducts in DNA (Hecht 2003). 2'-Hydroxylation of NNN, another important TSN, can give rise to the same intermediate as is formed by methyl hydroxylation of NNK, resulting in pyridylloxobutylation of DNA. The areca nut-specific nitrosamines (ASNAs) N-nitrosoguvacoline (NG) (Wenke et al. 1984; Nair et al. 1985; Stich et al.1986; Nair et al. 1987a) and the carcinogenic 3-(methyl-N-nitrosamino)propionitrile (MNPN).

6.2 Tobacco Smoking
Tobacco smoke contains more than 4000 chemicals, including material with carcinogenic, cytotoxic and mutagenic properties to the death of millions of patients. Tobacco being an independent risk factor, the relative risk of occurrence of OC in tobacco users is 11 times that “there is sufficient evidence that the use of smokeless tobacco can cause oral cancer in humans and that chewing tobacco may increase the risk for oral cancer development”.

It was estimated that a betel quid-chewing patient consumes 310,000 pieces of betel quid and a smoking patient consumes 14,000 packs of cigarettes before the diagnosis of oral cavity cancer on average. Besides, betel quid chewer and cigarette smoker were more prone to be diagnosed (Scheifele et al., 2007), with oral cavity cancer at a younger age than abstainers (Tsai et al., 2009).

6.3: Smokeless Tobacco (ST)
In a few countries of the Eastern Mediterranean Region, such as Sudan, Yemen and Pakistan, locally made or produced smokeless tobacco (ST) products are widely consumed. In other countries such as Egypt, the most populous Arab country, ST use has markedly increased among adults, according to the Global Adult Tobacco Survey (GATS) (WHO GATS survey 2010).

Smokeless tobacco is used in different forms in different parts of the world and approximately 150 million people use it worldwide. There are two main types of ST: chewing tobacco and snuff. Chewing tobacco in the form of loose leaf, cut, or shredded tobacco is universally available. Snuff for oral application, “dipping”, or sucking is dry or moist and is commercially available as loose or as portion bag packed products [Pindborg et al. 1992]. Although it is banned by governmental regulation in some countries, ST for oral use is manufactured and consumed on all continents [IARC 2007, Gupta et al 2003] under various names including betel-quid, chimo, gudhaku, gutkha, gul, iq’ milk, khitwam, kahaini, maras, maras powder, mishri, nass, naswar, plug, shamma, toombaak, moist snuff, snus, or some other variant depending upon the local production.

The term smokeless tobacco will be used to describe the habitual use of unburned tobacco products in the oral cavity. Shamma is a preparation of smokeless tobacco (Scheifele et al 2007), being a mixture of powdered tobacco, carbonate of lime, ash, black pepper, oils and flavoring. Shamma is used without burning the product, and can be used orally or nasally. Internationally, there are more than twenty eight types of orally used and two types of nasally inhaled ST (Rodu and Jansson, 2004). The location of shamma in the oral cavity has been reported as being: retained in the buccal cavity (1); kept in the vestibule of the mouth (2); allowed to rest in the gingivobuccal sulcus (3); placed in the lower labial or buccal vestibules.

The elongated period chewing of tobacco or the use of snuff has been associated with cancer of oral cavity, cheek, gums and oropharynx (Willis et al. 2012; Foulkes et al. 2013).

Table 1: Types of ST. Differences were Stated Based on the Country of Uses (Rashad et al 2014).

<table>
<thead>
<tr>
<th>Country</th>
<th>Local name(s)</th>
<th>Method of preparation</th>
<th>Method of use</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Yemen</td>
<td>Shammah</td>
<td>Mixture of powdered tobacco, carbonate of lime, ash, black pepper, oils and flavoring.</td>
<td>Placed in the buccal cavity, retained in the vestibule of the mouth.</td>
<td>(Allard et al., 1999)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Shamah</td>
<td>Mixture of powdered tobacco, carbonate of lime, ash, black pepper, oils and flavoring.</td>
<td>Placed in the mouth as a quid</td>
<td>(Allard et al., 1999)</td>
</tr>
<tr>
<td>Sudan</td>
<td>Toombak</td>
<td>Toombak is of the species Nicotiana rustica, and the fermented ground powder is mixed</td>
<td>Toombak is rolled into a ball that weighs about 10 g and is called a</td>
<td>(Idris et al., 1998)</td>
</tr>
</tbody>
</table>
Khat chewing is a widespread practice in Yemen, Ethiopia, Somalia, and Kenya. Khat is a plant whose leaves are chewed for its stimulant effect (Cigarette smoking and shamma (smokeless chewing tobacco) are used along with Khat in Yemen (Sawair et al., 2007; Scheifele et al., 2007). About 60% of those with OC were chewers (Sawair et al., 2007). Since most of the Khat chewers also chewed tobacco or smoked and consumed alcohol it was not possible to separate the effect of Khat chewing and other known risk factors in development of oral cancer. Khat has been shown to induce dominant lethal mutations in mice, embryotoxic and teratogenic effects in rats, as well as oral cancers in humans (Tarig et al. 1990, Islam et al., 1994).

6.5. Genetic Factors
Genetic instability, either spontaneous or mutagen induced, has been regarded as a predisposing factor for neoplastic transformation (Patel et al 2010). Cancer is the result of DNA mutations occurring spontaneously and from the action of different mutagens.

Chromosomal breaks has been reported in oral exfoliated cells in chewers of betel quid with or without tobacco. Micronucleus formation has been observed in precancerous lesions of the oral cavity of chewers (Nair et al. 1991). Mutations in the H. ras are more frequent in oral cancers of betel quid chewers (Saranath et al 1999) than those in western countries and Japan (Yeudall et al. 1993, Matsuda et al. 1996). K-ras mutations have been reported in oral cancers of betel quid chewers in Taiwan (Kuo et al 1994).

6.6 Socioeconomic conditions
Studies on the association of socioeconomic status (SES) and oral cancer have been somewhat conflicting. A review of oral cancer incidence and mortality in different socioeconomic levels around the world concluded that most studies did not show a clear trend in terms of incidence but excess mortality was observed for lower socioeconomic conditions in various populations (Faggiano et al 1997). Other studies have shown a decreased risk of oral cancer with higher SES based on occupation (Elwood et al 1984), and higher education levels (Ferraroni et al 1989). Individuals with low income were more likely to chew tobacco, smoke cigarettes, drink alcohol, eat less fruits and vegetables and have lower BMI.

6.7 Viral Infection
Infection can be induced by bacteria, virus and fungus. Periodontal disease has been shown to increase the risk of oral cancer. Viral infections play a role in the causation of oral cancers. The most common viruses associated with oral cancers are Human simplex virus (HSV-1), Epstein Bar virus (EBV) and Human Papilloma virus (HPV) types 16 and 18 (Yang et al 2004). More than 100 types of human papilloma viruses (HPV) have been identified. There are in vitro experiments that have shown that malignant transformation of oral keratinocytes can be caused by a sequential, combined effect of “high-risk” (HR) HPV and tobacco-related carcinogens [Kim et al. 1993]. The HPV induced cancers are biologically different from those related to alcohol and tobacco and most studies conclude that HR-HPV-related oro-pharyngeal SCC have a better prognosis and the therapy could be different, less aggressive as HPV positive tumors appear to be more susceptible to radiation [Ang and Harris et al 2010, Ragin et al 2007, Dayyani et al 2010]. Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer. Schwartz et al, reported a multiplicative effect of smoking and HPV, as measured by antibodies against HPV16.

7. Mortality and Survival
The survival rate reported in oral cancer patients is the lowest when compared to the other major cancers such as the cancer of breast, skin, testis, prostate, uterus and urinary bladder (Pisani et al., 1999) The number of new cases of oral cavity and pharynx cancer was 11.1 per 100,000 men and women per year. The number of deaths was 2.4 per 100,000 men and women per year. These rates are age-adjusted and based on 2009-2013 cases and deaths. The overall 5-year survival rate is 62% in industrial countries, while in developing countries they hardly reached the rate of 30% [Konstantin 2016]. The death rate associated with this cancer is particularly high not because it is difficult to detect or diagnose, but due to the cancer being routinely diagnosed late.
Figure 5: Mortality from oral cavity cancer among countries of the world (Source: Based on GLOBOCAN 2002 International Agency for Research on Cancer http://www.depdbdb.iarc.fr/globocan2002.htm)

Figure 6: Mortality from oral cavity cancer among women expressed by level of Age-standardized rate in countries of the world (Source: Based on GLOBOCAN 2002 International Agency for Research on Cancer http://www.depdbdb.iarc.fr/globocan2002.htm)

8. REFERENCES


