

REVIEW

Epidemiology of Oral Cancer in Asia in the Past Decade- An Update (2000-2012)

Sree Vidya Krishna Rao¹, Gloria Mejia¹, Kaye Roberts-Thomson¹, Richard Logan²

Abstract

The prevalence of oral cancers (OC) is high in Asian countries, especially in South and Southeast Asia. Asian distinct cultural practices such as betel-quid chewing, and varying patterns of tobacco and alcohol use are important risk factors that predispose to cancer of the oral cavity. The aim of this review is to provide an update on epidemiology of OC between 2000 and 2012. A literature search for this review was conducted on Medline for articles on OC from Asian countries. Some of the articles were also hand searched using Google. 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. The mean age of occurrence of cancer in different parts of oral cavity is usually between 51-55 years in most countries. The tongue is the leading site among oral cancers in India. The next most common sites in Asian countries include the buccal mucosa and gingiva. The 5 year survival rate has been low for OC, despite improvements in diagnosis and treatment. Tobacco chewing, smoking and alcohol are the main reasons for the increasing incidence rates. Low socioeconomic status and diet low in nutritional value lacking vegetables and fruits contribute towards the risk. In addition, viral infections, such as HPV and poor oral hygiene, are other important risk factors. Hence, it is important to control OC by screening for early diagnosis and controlling tobacco and alcohol use. It is also necessary to have cancer surveillance at the national-level to collect and utilise data for cancer prevention and control programs.

Keywords: Oral cancer - epidemiology - incidence - mortality - socioeconomic conditions - risk factor

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Introduction

Oral cancers (OC) are malignant lesions occurring in the oral cavity that include squamous cell carcinomas (SCC), salivary gland and odontogenic neoplasms. The majority (84-97%) of OCs are SCCs (Bhurgri et al., 2003; Sawair et al., 2007; Ariyoshi et al., 2008; Kruaysawat et al., 2010) which arise from pre-existing "potentially malignant" lesions or more often from normal appearing epithelium. OC spreads locally involving perioral structures and metastasises to local regional lymph nodes. The disfigurement consequential of the disease and treatment is permanent affecting the quality of life. This chronic disease is a public health problem both in developing as well as developed countries. The burden of OC is great because of the associated high cost of treatment, permanent impairment and high mortality. The prevalence of OC 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. The incidence rate of OC is rising in Asia. Furthermore, in Asian countries changes are being observed in a number of factors including site of occurrence, male to female ratio, age and occurrence in people with no known risk habits. An update on epidemiology of oral cancer is necessary to understand changing trends in the occurrence of the disease and its risk factors. Therefore, this narrative review has been presented with aim to provide an update on epidemiology of OC between 2000 and 2012.

Methods

Literature search for this review was conducted on medline for articles on oral cancer from Asian countries. The terms included "oral cancer" that was common along with other terms like "risk factors", "developing countries", "trend", "diet", "systemic conditions", "socioeconomic conditions", "education", "literacy", "human papillomavirus", "tobacco", "alcohol", "quid" using the preposition "and" between two terms. The

¹Australian Research Centre for Population Oral Health, ²Oral Pathology, School of Dentistry, Adelaide, South Australia, Australia
*For correspondence: sree.rao@adelaide.edu.au

filters included were 'humans', 'English only' and from '2000-2012'. Some of the articles that provided data on OC from Asian countries were also hand searched and internet-based using Google as a search engine.

The published articles available were mainly from India, Pakistan, Sri Lanka and Taiwan. Very few articles were from China, Thailand, Iran, Turkey, Yemen, Japan, Vietnam, Israel, Indonesia, Jordan, Philippines and Myanmar. Articles were excluded if the data on OC was combined and presented as head and neck cancer.

Incidence

OC is ranked one of the sixth most frequent malignancies in Asia. Nearly 274,300 new OC cases occur each year. High incidence rates are reported from developing nations situated in South-Central and South-East regions like India, Pakistan, Bangladesh, Taiwan and Sri Lanka. In India one third of the total cancer burden is attributed to OC (Parkin et al., 2005). In India and Pakistan 8-10% of all cancers occur in the oral cavity (Sunny et al., 2004; Bhurgri, 2005), with an incidence rate of more than 10 per 100,000 (Franceschi et al., 2000; Bhurgri et al., 2002). The age standardised incidence rate (ASIR) per 100,000 populations is least in China and highest in Sri Lanka (Ferlay et al., 2001; 2010). Whilst ASIR in Sri Lanka, Taiwan, Bangladesh, India and Pakistan exceed the world ASIR (10.5 for men and 4.02 for women), the ASIRs of Thailand, Hong Kong, and Singapore are well below that (Ferlay et al., 2001). As observed in Taiwan, the 7 year (1996-2002) average ASIR per 100,000 person-years was 25.74 for males and 3.61 for females (Chiang et al., 2010). In India, ASIR of 12.7/100,000 in men (Bombay) and 10.0/100,000 in women (Bangalore) has been reported (Franceschi et al., 2000). Other countries like Hong Kong, Philippines, Singapore, Japan, Vietnam, China and Israel have comparatively low incidence rates of less than 6/100,000 in both males and females. Among them Israel has the least ASIR of 1.6 in men and 1.2 in women (Franceschi et al., 2000).

Trend

While an increasing trend has been observed in Pakistan, Taiwan and Khonkaen province of Thailand (Bhurgri, 2004; Chiang et al., 2010; Vatanasapt et al., 2011) an opposite, decreasing trend is seen in Philippines, Sri Lanka and Chiangmai province of Thailand (Reichart et al., 2003; Laudico et al., 2010; Ariyawardana and Warnakulasuriya, 2011). The trend for tongue cancers in Taiwan is increasing both in men and women (Ho et al., 2002). An increasing trend is seen for cancers of all the sites in the oral cavity except for the lip in Pakistan (Bhurgri, 2005). Surprisingly, OC in Taiwan increased five-fold among men and doubled in women from 1982-2001 (Su et al., 2007b). The trend in India shows variations in incidence rates between the registries. Over fifteen years (1986-2000) in a cancer registry in Mumbai (India), the incidence rate has decreased in men without any changes in women (Sunny et al., 2004). On the other hand, when all six registries are considered, the trend seemed to be

increasing in men (Yeole, 2007). On the whole, with changing lifestyle in India the trend is expected to rise and by 2016 the incidence is projected to be 1.5 times the rate in 2001 (Murthy et al., 2008).

Age and gender

OC is considered to be a disease that occurs mainly in the elderly. However, while most of the cases of OC occur between 50 and 70 years of age (Bhurgri et al., 2006), it still could occur in children as early as 10 years of age in the absence of any known risk factors (Khan and Naushad, 2011; Solanki et al., 2012). With advancing age, the number of people affected by OC increase (Ariyoshi et al., 2008). The mean age of occurrence of cancer in different parts of oral cavity is usually between 51-55 years in most of the countries but higher around 64 years, in Thailand (Bhurgri et al., 2006). Recently, there has been a shift towards younger age at diagnosis (Iype et al., 2001a; Iamaroon et al., 2004; Su et al., 2007a). About 17% of the younger patients are below 40 years of age (Halboub et al., 2011) or at least in the fourth decade of their life (Sherin et al., 2008).

Considering all the age groups, men are more affected than women. This is true when we observe male to female ratio which is 1.45 in Japan (Ariyoshi et al., 2008), 1.5 in Pakistan (Bhurgri et al., 2006), 1.65 in Yemeni patients (Halboub et al., 2011) and highest of 10.5 in Taiwan (Chiang et al., 2010). A few reports from one of the Indian registries and Pakistan show equal male to female ratio of 1 (Franceschi et al., 2000; Bhurgri et al., 2003). Some of the institutional studies from India report that OC occurred two to four times more commonly in men than women (Mehrotra et al., 2003; Gangane et al., 2007; Sherin et al., 2008; Sharma et al., 2010; Aruna et al., 2011). A reverse gender ratio is observed in India (Bangalore) and Thailand where male to female ratio is 1:2.0 and 1:1.56 respectively (Franceschi et al., 2000; Kruaysawat et al., 2010). Taking into account only young adults, men are predominantly affected (Iamaroon et al., 2004; Sherin et al., 2008).

Sites in Oral Cavity

The site of occurrence depends on the predominant risk factors in that particular geographical region. In recent years many countries report the tongue as the most frequently affected site. In Japan, Taiwan, Thailand, Yemen, India and Iran, the tongue is the foremost among all sites contributing up to 42% of all oral sites in adults of all ages (Dhar et al., 2000; Su et al., 2007a; Ariyoshi et al., 2008; Kruaysawat et al., 2010; Ibayashi et al., 2011; Razmpa et al., 2011). The tongue is the leading site not only among oral cancers but also among head and neck cancers in India (Addala et al., 2012). The next most common sites in Asian countries include the buccal mucosa and gingiva. Cheek or buccal mucosa cancers exceed all other oral cancers in other places like Pakistan, Uttar Pradesh state in India and Changua County in Taiwan (Bhurgri et al., 2003; Su et al., 2007a; Sharma et al., 2010). Lip cancers are less in Asian countries. Myanmar shows a different site predilection. Here cancers of the lip

and tongue follow cancers of gingiva and floor of mouth (Reichart and Way, 2006).

Young adults of 45 years or below suffer more from tongue cancer (Manuel et al., 2003; Ibayashi et al., 2011). Differences in site predilection were seen on comparing older (≥ 40 yrs) and younger adults (< 40 yrs). Older people have tendency to develop cancer of buccal mucosa whereas it is the tongue (60%), followed by buccal mucosa and other sites that is affected in the younger people (Iype et al., 2001a; Iamaroon et al., 2004; Sherin et al., 2008).

Recurrence

Recurrence is an important aspect of treatment outcome. It indicates a poor prognosis. According to an institutional study from India, the average disease free survival time is around 35 months (Priya et al., 2012). Retrospective analytical studies from hospitals present patterns of recurrence and the factors influencing it. Recurrence can be local, regional, locoregional or second primaries. Recurrence rates vary between 25-40% after a follow-up period of 2-4 years (Hakeem et al., 2012; Priya et al., 2012; Wang et al., 2012). Most recurrences are local (Hakeem et al., 2012; Priya et al., 2012). A considerable proportion of cases (34%) in Japan presented with second primaries (Shiga et al., 2011). The clinico-pathological factors that influence the treatment outcome and likelihood of recurrence are use of tobacco, advanced T stage or stage III-IV disease at diagnosis, including local regional nodal involvement, positive resection margins or the resection margins being very close to the tumour and thickness of tumour ≥ 7 mm (Battoo et al., 2012; Hakeem et al., 2012; Priya et al., 2012; Wang et al., 2012). Patients who are pathologically negative for local regional nodal involvement could present with regional metastasis later due to occult metastasis (Liu et al., 2010). Although adjuvant therapy reduces local recurrence it does not affect the overall recurrence (Battoo et al., 2012; Priya et al., 2012).

Mortality and Survival

Even with the technological advancement in treatment modalities and diagnosis, the 5 year survival rate has been low for OC. It is the most fatal of all cancer in men and fourth most fatal in women in the age group of 30-69 yrs in India (Dikshit et al., 2012). In Taiwan OC is fourth leading cause of death (Su et al., 2007a). OC associated premature mortality is 16-21 years in men and 14-22 years in women in Japan (Ibayashi et al., 2011), where increased numbers of cases are diagnosed at initial stages of the disease before any evidence of nodal involvement has occurred (Ariyoshi et al., 2008). In Taiwan, the overall survival is 61% (Liu et al., 2010). In rural India, relative survival is still lower. It is 38% and 42% for tongue and other areas of mouth respectively (Swaminathan et al., 2009). Patients with advanced stage of the disease have a higher mortality rate than those at the initial stages (Iype et al., 2001a; Iamaroon et al., 2004). The probability of survival in the presence of nodal involvement reduces from 80% for stage I to less than 20% for stage IV after

5 years following diagnosis (Ma'aita, 2000; Kruaysawat et al., 2010). The 5 year survival in the absence of nodal involvement decreases with increase in the tumour size from 95% for T1 to 25% for T4 cases (Ma'aita, 2000). As evidenced from a randomised controlled trial of screening for oral cancers in India, the mortality rate reduces with initial stages at diagnosis (Sankaranarayanan et al., 2000). Screening improves the survival by early diagnosis and provision of health care. At the individual level, tumour characteristics are important in determining the OC mortality (Cancela et al., 2009). Most of the cases spread regionally and distant spread is seen only occasionally (Bhurgri et al., 2003). Those cases with regional spread experience a threefold increase in mortality while those with distant metastasis have a sixfold excess risk (Yeole et al., 2000).

Subsequent to diagnosis, the treatment provided based on the stage at diagnosis could influence the survival. Survival following surgical treatment depends on the pre-operative characteristics of tumour including positive nodes, thickness of the tumour ≥ 7 mm, poorly differentiated tumour, the surgery itself, performance of neck dissection and post-operative positive resection margins (Lo et al., 2003; Manuel et al., 2003; Liu et al., 2010). Those patients treated by radiotherapy alone for advanced stage of disease have a shorter survival (Sargeran et al., 2008).

In Iran there is no age-wise or gender-wise difference in survival when cases of all age groups are taken in account. Japan's mortality rate related to mouth cancer is seen to increase among the younger birth cohort (Marugame and Sobue, 2004). In young adults (< 45 years) 5 year overall survival is 78% and 5 year disease free survival is around 57% (Manuel et al., 2003). There is no significant difference in survival between young male and female adults affected by tongue cancer (Iype et al., 2001a), but those below 35 years have survival rate lower than any other age group (Yeole et al., 2000). Mortality related to tongue cancer exceeds that of buccal mucosa (Iype et al., 2001a; Iamaroon et al., 2004). Lip cancer has a very good prognosis with the lowest mortality rate (Iype et al., 2001a). The 5 year survival rate is 74.5% for lips, 42.7% for anterior tongue, 25.5% for posterior tongue, 45% for other areas of mouth and 30% for oro-pharynx (Yeole et al., 2000).

Other than cancer related factors there are several more that can influence mortality, for example, personal habits like tobacco use, betel quid chewing and alcohol consumption are associated with high mortality in OC patients (Lo et al., 2003; Cancela et al., 2009). Alcohol consumption independently affects survival (Liu et al., 2010). These habits interact with dietary intake of nutritious food. Co-existence of smoking and tobacco chewing in drinkers is highly apparent in those consuming less vegetables and fruits (Cancela et al., 2009). Better pre-operative nutritional status helps in improving the survival of OC patients (Liu et al., 2006). The situation may be further complicated by poor socio-economic conditions. Living in a disadvantaged neighbourhood with low individual socioeconomic status (SES) and having less or no education reduces the probability of

survival (Yeole et al., 2000; Dikshit et al., 2012; Lee et al., 2012). At the national level, factors like life expectancy, gross national product, literacy rate, health expenditure, physician density and efficiency of health care system have a formative role in controlling the oral cancer mortality (Sargean et al., 2008).

Published data available from different Asian countries on incidence, trend, male to female ratio, site predominantly affected and overall 5 years survival have been summarised on Table 1.

Risk factors

Socioeconomic conditions (SEC)

OC, similar to many other chronic diseases exhibits a social gradient. At a country level the ASIRs are higher in developing countries compared to developed countries. There are a few published studies from Asian countries that have looked into socioeconomic conditions (Warnakulasuriya, 2009). A meta-analysis of 41 case-control studies across the globe has demonstrated that low SEC is an independent risk factor for oral cancer (Conway et al., 2008). People doing manual occupations such as agriculture, labouring, and working in industries, are at increased risk for developing OC (Dhar et al., 2000; Balaram et al., 2002; Muwonge et al., 2008). In Sri Lanka, for example, tea estate workers are a high risk population (Ariyawardana et al., 2007). Odds ratio (OR) of 2.5-2.8 has been calculated for development of OC among farmers in India (Subapriya et al., 2007; Madani et al., 2010a; Pawar et al., 2012).

Studies from India, Pakistan and Turkey show an association between education and OC. Illiterates (Balaram et al., 2002; Rajkumar et al., 2003; Subapriya et al., 2007; Muwonge et al., 2008), those who never attended school (Merchant et al., 2000) and with low educational attainment (Guneri et al., 2005) have greater risk. In the Indian population OR for OC related to education is greater for illiterates (6.4) (Subapriya et al., 2007) compared to low education level (5.3) (Madani et al., 2010a). However, another study from India failed to

show low education as risk factor after controlling for age and habits (Dikshit and Kanhere, 2000). In a South Indian cohort, education was related to OC only in men and not women (Jayalekshmi et al., 2009; 2011).

In Asian countries where OC is highly prevalent, the proportion of people living below national poverty line range between 22 and 44% (Knowles, 2000). In Pakistan increasing incidence of OC from 1995-2002 was consistently highest in the lower income group (Bhurgri, 2005). Contrary to this finding, low income was not found to be a risk factor in a Turkish population (Guneri et al., 2005). A case control study from India demonstrates the presence of an association with low income. The estimated odds ratio associated with monthly household income of less than Rs 5000 was 1.7 (Madani et al., 2010a). Low SEC may be interrelated with other factors like nutrition, health care, living condition and risk behaviours contributing to the development of OC (Warnakulasuriya, 2009).

Quid chewing

Quid chewing is an ancient ethnic practice in Southeast Asian countries. Betel quid is chewed owing to its medicinal properties (Raghavan and Baruah, 1958) and as a symbol of social life. 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. The causal link between chewing quid without tobacco and carcinogenesis has been recognised (Merchant et al., 2000). Areca nut used in betel quid is known to cause OC due 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). Betel quid in Taiwan does not contain tobacco (Chiang et al., 2010) unlike in other countries such as India, Pakistan, Bangladesh and Vietnam, where quid mostly contains

Table 1. A Summary Table Showing Data on Oral Cancer Various Outcome Estimates Available from Various Asian Countries from 2000* to 2012

Country	Incidence (ASIR)		Trend	Male: Female	Predominant site	Overall 5 year survival
	Males	Females				
India	12.6	7.3	Increasing	0.5-1	Tongue/Buccal mucosa	38-42%
Pakistan	21.3	19.3	Increasing	1-1.5	Buccal mucosa	-
Sri Lanka	16.5	5	Decreasing	-	-	-
Taiwan	25.7	3.61	Increasing	10.5	Tongue/Buccal mucosa	61%
China	1.4	0.7	-	-	-	-
Thailand	3.9	6.2	Increasing (in Khon Kaen) Decreasing (in Chiangmai)	0.64	Tongue	18.2-43.1%
Iran	-	-	-	-	Tongue	-
Israel	1.6	1.2	-	-	-	-
Yemen	-	-	-	1.65	-	-
Philippines	3.4	2.9	Decreasing	-	-	-
Japan	-	-	-	1.45	Tongue	-
Singapore	6.2	2.2	-	-	-	-
Hong Kong	7.4	3.1	-	-	-	-

*No data available from Bangladesh and Vietnam

tobacco (Merchant et al., 2000; Balaram et al., 2002; Reichart and Nguyen, 2008). Despite this the incidence rate of OC is very high in Taiwan (Chiang et al., 2010), especially among men chewing quid habitually, with an OR of 10.97 (Yen et al., 2008; Lin et al., 2011). In a South Indian population, a substantial increase in risk (OR 4.2 in men and 16.4 in women) was observed among chewers of quid without tobacco and it was even greater in those who chewed quid with tobacco (OR 6.1 in men and 45.9 in women) (Balaram et al., 2002). A few other studies from India and Pakistan exhibit similar results (Merchant et al., 2000; Muwonge et al., 2008). Thus, addition of tobacco to quid further enhances the risk.

In addition, starting to chew the quid before 20 years and chewing ≥ 10 quids per day increases the risk. A dose response relationship exists for number of quids chewed in a day and the risk persists even after quitting the habit (Balaram et al., 2002). Usually after chewing quid with tobacco the fluid is spat out. By swallowing the fluid after chewing and retaining quid in mouth overnight, the risk is increased to a great extent (Gangane et al., 2007; Muwonge et al., 2008). Quid chewing with or without tobacco has greater role to play in causing cancer in other areas of mouth than the tongue (Znaor et al., 2003). Smoking and/or consuming alcohol along with quid chewing inflates the risk in men and hastens the carcinogenesis resulting in early age of onset of OC (Yen et al., 2008; Lee et al., 2011). The OR for chewing quid as well as smoking in men of Taiwan is very high, exceeding 26.5 (CI 14.52-48.58) (Lin et al., 2011).

Tobacco Use

Smoking

Tobacco use is widespread in Asian countries. More than 90% of OC cases report using tobacco products (Balaram et al., 2002; Madani et al., 2010b). Tobacco being an independent risk factor, the relative risk of occurrence of OC in tobacco users is 11 times that of people who never used tobacco (Madani et al., 2010b). It is used in smoking as well as smokeless forms. Smoking includes use of cigarettes, bidi and hookah. Though cigarette smoking is seen in all Asian countries, bidi smoking is common in countries like India, Pakistan and Sri Lanka. Bidi is prepared by rolling dried tobacco flakes into a dried Temburni leaf (*Diospyros melanoxylon*) and secured with thread (Sanghvi et al., 1955). Smoking bidi is an important risk factor contributing to a considerable number of oral cancer cases in India, Bangladesh, Nepal, Pakistan and Sri Lanka (Rahman and Fukui, 2000). Bidi smokers are 4 times at risk of developing oral cancer compared to non-smokers (Madani et al., 2010b). A meta-analysis of 12 studies from India, Sri Lanka and Pakistan on bidi smoking and oral cancer clearly demonstrated dose-response relationship for the duration of bidi smoked. However, no significant relationship was observed with cigarette smoking (Rahman et al., 2003; Gangane et al., 2007; Muwonge et al., 2008; Madani et al., 2010b; Jayalekshmi et al., 2011) except in Chidambaram, India, where cigarette exhibited increased risk (OR 2.33) but lower than bidi smokers (OR 4.63) (Subapriya et al.,

2007). This could be due to poor combustibility as well as the nicotine and tar content of bidi which exceeds that of cigarette (Rahman and Fukui, 2000). Bidi smokers have 3.1 times increased risk for oral cancer compared to non-smokers in South Asia (Rahman et al., 2003; 2005). It could be possible that this is because more toxic products are emitted and inhaled by bidi smokers (Rahman and Fukui, 2000). Bidi smoking is more widely practised by people of lower socioeconomic strata. Since bidis are cheaper than cigarette people of lower socioeconomic class and from rural areas use bidis more. In such populations interaction with other risk factors could enhance the effect of bidi smoking. Tobacco smoking associated risk is higher for women (OR 3.2) compared to men (OR 1.8) (Balaram et al., 2002). Commencing smoking after 20 years of age did not increase the risk for OC. Current smokers have increased risk compared to past smokers (Muwonge et al., 2008). Quitting smoking for more than 10 years slightly declined the risk (Balaram et al., 2002). Not only the number and duration of smoking but also the toxicity of type of cigarette used has to be considered. Local cigarettes not complying with the international standards and emitting high tar and nicotine can pose a high risk (Guner et al., 2005). On the whole, risk for daily smokers is three times that of non-smokers (Madani et al., 2010b). Contrary to this, in a Karunagapally cohort (India) bidi smoking did not show any risk for oral cancer in tobacco chewers but an elevated risk was observed with bidi smoking when analysis was restricted to non-tobacco chewing smokers (Jayalekshmi et al., 2011). It appears that tobacco chewing has a stronger effect than bidi smoking, masking the effect of bidi in the chewers. The number of bidis smoked per day, a longer duration of smoking and a younger age at starting to smoke was associated with OC (Jayalekshmi et al., 2011). Tongue cancer risk increased for those who smoked bidis for more than 30 years (Jayalekshmi et al., 2011). In rural areas where smoking is low, there is a low incidence of oral cancer (Thorat et al., 2009). In a population based study at Bhopal, India a linear increase was seen with number of bidis and cigarettes smoked per day (Dikshit and Kanhere, 2000). A significant dose response relationship has been observed with the duration and number of sticks of cigarette and bidi smoked per day (Subapriya et al., 2007).

Smokeless tobacco (SLT)

SLT is used in a variety of forms, is widespread among both men and women. Common forms include tobacco flakes, whole leaf in India, Nass/ Naswar in Pakistan and other countries of Asia, Zarda in Bangladesh and Shamma in Saudi Arabia. Other recent forms that are available since the introduction into the Indian market in 1980s are panmasala and gutkha used by old and young similarly (Nair et al., 2004). Panmasala and gutkha are blends of tobacco, areca nut, lime and catechu. The combination of ingredients is strongly genotoxic and carcinogenic (Nair et al., 2004). Dose response relationship has been observed with daily frequency and duration of tobacco chewing (Subapriya et al., 2007). Difference in risk by sub-site demonstrates that gingival and buccal/ labial cancer

have a linear dose response relationship with duration and frequency but risk for tongue cancer increased with chewing tobacco for ≥ 15 times in a day (Jayalekshmi et al., 2011). In men, only chewing tobacco had a stronger risk (5.4 times) than those who never chewed (Jayalekshmi et al., 2011). In women it is still higher (Muwonge et al., 2008; Jayalekshmi et al., 2009). Women chewing tobacco 10 or more times a day have risk 9.2 times that of non-tobacco chewers irrespective of age of initiation of tobacco chewing (Jayalekshmi et al., 2009).

Qat chewing is a widespread practice in Yemen. Qat is a plant whose leaves are chewed for its stimulant effect (Scheifele et al., 2007). Cigarette smoking and shamma (smokeless chewing tobacco) are used along with qat 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 qat chewers also chewed tobacco or smoked and consumed alcohol it was not possible to separate the effect of qat chewing and other known risk factors in development of oral cancer. SLT users are at greater risk than those smoking tobacco (Muwonge et al., 2008; Madani et al., 2010b). OC is largely associated with gutkha followed by tobacco flakes (Madani et al., 2010b). Gutkha and panmasala are termed 'polyingredient oral dip products' and are more carcinogenic because of other carcinogenic compounds present and most of it is dry weight (Madani et al., 2012), lacking the protective effect of betel leaf (Amonkar et al., 1989). This could be due to contact of tobacco and other carcinogenic compounds being kept in contact with oral mucosa for a considerably longer time. A greater incidence of OC is observed in Asian societies where consumption of SLT is high. In a study conducted in Kerala tobacco chewing was a greater risk for gum and mouth cancer but slightly less so for tongue. Mishiri, a tobacco product applied as a tooth cleaner also has been shown to increase the risk after adjusting for other types of tobacco use in Indian population (Madani et al., 2012). Tobacco chewing exhibited a linear relationship with risk of development of oral cancer (Dikshit and Kanhere, 2000). Those who chewed tobacco were also found to smoke heavily further exaggerating the risk (Dikshit and Kanhere, 2000; Gangane et al., 2007; Jayalekshmi et al., 2011).

Tobacco chewing is a stronger risk factor for oral cancer than smoking where chewing is a prevalent practice as stated above (Lin et al., 2011). Evidence from an Indian study, however, differed; it was found that OR for OC due to bidi smoking was 7.45 while OR due to chewing tobacco was 4.10 (Subapriya et al., 2007).

Alcohol Consumption

Drinking alcohol is an important risk factor for oral cancer. In China, India, Pakistan, Sri Lanka, Bangladesh, Nepal and Thailand spirits are consumed more commonly, while beer consumption is more common in Turkey, Myanmar, Malaysia and Indonesia (WHO, 2011). Geographic variation in the most prevalent type of alcoholic beverage consumed determines the type of alcohol contributing to the occurrence of oral cancer in that particular region. Alcohol use may be under-reported

in communities where alcohol consumption is restricted (Merchant et al., 2000). In China, where drinking is a part of festivals and celebration (Cochrane et al., 2003) OC is significantly related to alcohol consumption (Li et al., 2011). A prospective study in India has found that alcohol consumption increases the incidence by 49% among current users and 90% in past drinkers (Cancela et al., 2009). This could be due to residual effect of alcohol consumption or them having quit the habit due to serious illness. Consumption of alcoholic beverages was associated with increased risk for OC in men (OR 2.2) but the same was not observed in women (Balaram et al., 2002). This was because very few women consumed alcohol. Risk increases with number of drinks consumed in a week (Balaram et al., 2002; Muwonge et al., 2008). More than 70% of the cases consumed locally prepared and hard liquors like toddy or arrack in India (Balaram et al., 2002) and raki in Turkey (Guneri et al., 2005). The age of starting to drink and cessation of the habit did not influence the risk (Balaram et al., 2002). Alcohol consumption was not associated with increased risk in men of a Kerala cohort even among despite tobacco use (Jayalekshmi et al., 2011). Contradictory results have been obtained in other studies. Alcohol has a synergistic effect with tobacco chewing and smoking (Gangane et al., 2007; Subapriya et al., 2007; Muwonge et al., 2008; Lin et al., 2011). In Taiwan a prospective study found no statistically significant increase in risk for those who consumed only alcohol but the increase was 40 fold in people chewing and smoking. The risk was less if they either smoked or chewed along with drinking (Lin et al., 2011).

Diet

Diet is influenced by the culture of a population. The complexity of the diet makes it difficult to assess the role of dietary components in cancer development. Research has been conducted in terms of assessment of dietary pattern and nutrition. There are no well-designed epidemiological studies from Asian countries regarding this aspect. A few studies have been able to show some relation with OC. Outcomes of factor analyses of dietary pattern and OC conducted in Indonesia and Malaysia are similar. Increased risk was seen with high consumption of combination (meat/by-products, dairy, fermented/salted food) and traditional food (starch and beverages) whereas a protective effect was observed with a prudent diet (fruits and vegetables) after adjusting for habits (Amtha et al., 2009; Helen-Ng et al., 2012). Polycyclic Aromatic Hydrocarbons (PAH) present in the environment are carcinogens, they are present in high concentrations in meat products (Xia et al., 2010). Therefore, if present in the diet may move entry into the human body from the environment (Xia et al., 2010). In a Turkish population, margarine and egg consumption was associated with increased risk while fish and raw vegetables decreased the risk for OC (Guneri et al., 2005). An Indian study also demonstrated that fish and milk conferred a protective effect (Rajkumar et al., 2003; Gangane et al., 2007). The protective effect of fruits and vegetables on OC is unequivocal. Risk of OC for non-vegetarians is greater

than vegetarians by 85% (Subapriya et al., 2007). This could be attributed to reduced exposure to PAHs among non-vegetarians compared with vegetarians and so contributes to the increase in risk for OC. However, the OC risk attributable to dietary PAH exposure is still unclear.

Viral Infections

Viruses also play a role in the aetiology of OCs. Various viruses have been investigated in this context including Epstein Bar Virus (EBV), Human Simplex Virus-1 (HSV-1) and Human papilloma virus (HPV) types 16 and 18 (Shimakage et al., 2002; Yang et al., 2004). The strongest association is between HPV and squamous cell carcinoma of the oral cavity and more so in the oropharynx (Parkin et al., 2008). There is sufficient evidence for a causal role of HPV-16 in this context but it is limited for HPV-18 (Herrero et al., 2003). These viruses are found in approximately 25% of cases in India to 85.7% in Taiwan (Chen et al., 2002; Nagpal et al., 2002). In Taiwan high risk HPV (Subtypes 16 and 18) emerged as independent risk factor even after adjusting for age, gender, cigarette smoking and low risk HPV infection. The OR for OC due to HPV-16 (11.21) is greater than that for HPV-18 (Chen et al., 2002). In a Malaysian population, the OR was lower (4.3) (Saini et al., 2011). HPV is less common in cases that chewed quid or smoked when compared to those who had had multiple sexual partners (Chen et al., 2002). Contracting HPV infection by practising oral sex is very likely in men increasing the risk of OC 3 fold (Rajkumar et al., 2003). HPV acts synergistically with betel quid chewing to cause high morbidity (Chen et al., 2002). HPV-16 infection is more common than HPV-18 (Nagpal et al., 2002).

Oral Hygiene

Poor oral hygiene has been advocated as a risk factor for oral cancer. This has been assessed by measuring tooth loss or status of the dentition and periodontal disease. Poor general oral condition associated with increased risk in both genders (Balaram et al., 2002; Subapriya et al., 2007). In one study, more than 85% of OC patients had poor oral hygiene (Dhar et al., 2000). Poor oral hygiene related attributable risk is around 32% for men and 64% for women in India (Balaram et al., 2002). In long term denture wearers using ill-fitting dentures, the oral mucosa is subjected to chronic irritation. It has been reported that the been wearing dentures for more than 15 years and not visiting a dentist regularly was highly associated with OC (Guner et al., 2005).

Family History of Malignancy

Family history of malignancies could be a risk factor. Though there is no substantial evidence from well-designed studies, the plausibility cannot be ignored and needs to be explored. A case series of young adults from India and Thailand revealed that 30 to 40% of them have no known risk factors. Positive family history of malignancy is present in 2.4 to 14% of young oral cancer patients (Iype et al., 2001a; Iamaroon et al., 2004) and a positive family history of OC in young adults was 2.6% (Iype et al., 2001b).

Diabetes Mellitus

Prevalence of diabetes mellitus (DM) is increasing in Asia. India and China are the two major contributors to the increasing prevalence of type II diabetes in Asia.

Table 2. A Summary Table Showing Data on Risk Factors for Oral Cancer Available from Various Asian Countries from 2000-2012*

Country	Risk factors	Country	Risk factors
India	SEC	Turkey	SEC
	Quid with and without tobacco (Paan)		Smoking cigarette
	SLT		Alcohol
	Bidi and cigarette smoking		Diet
	Alcohol	Bangladesh	Bidi
	HPV		Bidi
	Diet	Yemen	Qat
Family history of cancer		Quid with tobacco (Shammah)	
Sri Lanka	SEC		SLT
	Smoking with and without tobacco		Smoking
	Bidi smoking	Indonesia	Diet
Pakistan	SEC		Malaysia
	Quid with and without tobacco (Paan)		Diet
	SLT	Thailand	Quid with tobacco
Bidi smoking	Smoking		
Taiwan	SEC		Alcohol
	Quid without tobacco		Family history of cancer
	Smoking	Philippines	Quid
	Alcohol		Smoking
	HPV	Vietnam	Quid with tobacco
Heavy metals			

*Data on table 2 are not ranked

The metabolic disorder occurs at least a decade earlier in developing countries than developed countries affecting the younger population (Ramachandran et al., 2010). An association between DM and OC has been proposed. A randomised controlled trial conducted in Kerala, India found an association between DM and pre-malignancies like leukoplakia (OR 2.0) and erythroplakia (OR 3.2) in women but not in men (Dikshit et al., 2006). On the contrary, DM was not a risk factor for OC when adjusted for age, other co morbidities, residential location and occupation (Tseng, 2012). Lack of unequivocal evidence warrants further investigations.

Others

Heavy metals

There is a high incidence of OC that is not explained by the life style factors such as betel quid chewing or cigarette smoking in Taiwan. The spatial correlations suggest that heavy metals such as chromium and nickel found in the soil may have roles to play in the complex aetiology of OC (Chiang et al., 2010). Further studies are warranted to investigate the relationship between heavy metals in the soil and OC.

The Table 2 summarises the published data on risk factors available from various Asian countries between 2000 and 2012.

Conclusion

This review has drawn data from published articles which differ in study designs, to narrate the scenario of epidemiology of OC in Asian countries between 2000 and 2012. Comparability of estimates of OC outcomes is limited accounting to varying data collection methods used in the studies. There are dissimilarities in the incidence rates of OC across different countries in Asia. While there are some common factors like use of tobacco, alcohol and quid chewing there are some differences in the prevalence of habits, in addition to some still unknown or unexplained factors other than social and economic factors in these Asian countries. High incidence is particularly observed in Asian countries with a cultural practice of chewing quid. Recently available quid sachets like gutkha and panmasla are used by children, men and women alike and may increase OC incidence. Tobacco chewing along with smoking and alcohol are the main reasons for the increasing incidence rate of OC. Low SES and diet low in nutritional value lacking vegetables and fruits contribute towards the risk. In addition, viral infections, such as HPV and oral hygiene, are other important risk factors. The incidence of OC is increasing in most Asian countries; hence, it is important to undertake programs to prevent and control OC by screening for early diagnosis and enabling societies to support a tobacco free environment and moderate alcohol use. It is also necessary to improve the living standards of people and health care systems where access to health care is poor or limited. There is also need for cancer surveillance at national-level to collect and utilise data for cancer prevention and control programs.

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