CHAPTER 3

LITERATURE REVIEW

3.1 Terminology and classification of oral cancer

Defining oral cancer presents some important challenges to both clinicians and researchers. Unlike other areas of the body, the boundaries of the oral cavity are not always easy to delineate. The estimates of cancer occurring in the 'mouth' should be carefully evaluated after knowing the exact anatomical structures of the oral cavity and surrounding tissues. Oral cavity extends from the lips to the palatoglossal folds. The outer vestibule is enclosed by the cheeks and lips and forms a slit-like space separating it from the gingiva and teeth. The buccal mucosa extends from the commissure of the lips anteriorly to the palatoglossal fold posteriorly. The gingival mucosa surrounds the necks of the teeth and the alveolar mucosa overlies the alveolar bone and extends to the vestibular reflections (Slootweg and Eveson, 2005).

The hard palate is continuous anteriorly with the maxillary alveolar arches and posteriorly with the soft palate. The oral part of the tongue (anterior two thirds) lies in front of the V-shaped sulcus terminalis. It is mobile and attached to the floor of the mouth anteriorly by the median lingual frenum. The floor of the mouth is a horseshoe shaped area between the ventrum of the tongue medially and the gingiva of the lower teeth anteriorly and laterally. The floor of the mouth extends to the palatoglosal folds distally and is in continuity with the retromolar pad behind the lower third molar tooth. The oral cavity is lined by stratified squamous epithelium (Slootweg and Eveson, 2005).

The oropharynx lies behind the oral cavity. It is bounded superiorly by the soft palate and inferiorly by a hypothetical horizontal line level with the tip of the epiglottis. Anteriorly are the isthmus of the fauces and the posterior third of the tongue, and the lateral wall is formed by the palatopharyngeal arches and the palatine tonsils. The posterior wall contains the pharyngeal tonsils.

The term oral cancer has been used differently by many researchers. Some researchers have also used terminologies such as ‘mouth cancer’ or ‘head and neck cancer’ interchangeably with ‘oral cancer’. Moore et al. (2000a) stated that the term ‘mouth cancer’ seems more general and includes sites/sub sites in the oral cavity, such as lips and minor/major salivary gland (Moore et al., 2000a: Mc Cartan, 2001). Many attempts to define oral cancer have been made and as yet there seems to be no uniformly accepted definition of oral cancer. A review of oral cancer terminology for the period 1994 to 1999 was done by Moore et al (2000a). They showed that 18 studies used the term ’oral cancer’, 5 studies used ‘oral cavity cancer’, 2 studies used ‘mouth cancer’, 6 studies used ‘oral and pharyngeal cancer’ and the 7 remaining studies described ‘tongue and oral cavity’, ‘mouth and pharynx’, ‘buccal cavity and pharynx’, ‘lip, tongue and oral cavity’, lip, salivary gland and other oral cancers.

In order to be able to compare studies globally, the terminology for diseases should follow the International Classification of Diseases (ICD) coding system of the World Health Organization (WHO) for international databases for epidemiological survey of diseases including cancers. The ICD provides a detailed coding system based on the first primary anatomic site of the tumor. The organ within which the cancer first developed is assigned a three-digit code. A

fourth digit is available to provide further specification of the tumor's location within the organ. In addition, ICD codes are used for identifying cause of death, and therefore cancer mortality data can be easily extracted from vital record systems for analysis and comparison with incidence data (Pastides, 2001). As new versions of the ICD have been developed, registries have developed transmutation to allow researchers to equate newer codes for particular sites and thus extract computerized data for cancers of a particular anatomic site over several decades. Because the ICD codes for many cancers have not changed substantially from the 7^{th} through the 10^{th} revision, it is possible to conduct epidemiological analysis of long-term trends for these cancers worldwide.

The majority of data available have used ICD-9 system. This system describes malignant neoplasm of lip, oral cavity including salivary glands and pharynx together with codes 140-149, thus not reporting figures exclusively on oral cancer.

Most of the terminology of oral cancer adopted by many researchers include cancer of the lip (ICD-9 code 140), excluding the skin of the lip; cancer of tongue (ICD-9 141); gum (ICD-9 143); floor of the mouth (ICD-9 144); and other areas of mouth including buccal and labial mucosa, palate, uvula, retromolar areas and other unspecified areas (ICD-9 145). Cancer of major/minor salivary gland, nasopharynx (ICD-9 147), hypopharynx (ICD-9 148) and other buccal/pharynx (ICD-9 149) were excluded from the oral cancer terminology (Moore et al., 2000a).

However, even though the majority of researchers used the term ‘oral cancer’, different definitions can still be noted when references are made to ‘oral cancer’. For example; Johnson and Warnakulasuriya (1993a) used the term “oral cancer” (ICD-9 140-145) and included ICD-9 code 140 (lip) excluding the skin of the lip; ICD-9 141 (tongue) and ICD-9 143-5 (gum, floor of the mouth and other sites of oral cavity). MacFarlane et al., (1996) and Oji et al. (2006) used the term ‘oral cancer’ similar to Johnson and Warnakulasuriya but also included tonsil/naso and oropharynx (ICD-146 to 149). However, some other researchers used the term ‘mouth, oral cavity or intra oral cancer’ to mean ICD-9 140-141, 143-145 which are included as ‘oral cancer’ by others (Franceschi et al., 1992; Moore et al., 2000b). .

The difficulties of defining the term ‘oral cancer’ are caused by the difficulties in combining some sites and deciding the precise location of the tumor that extends over a number of anatomical structures. However, currently, there has been an increase in usage of the latest 10^{th} revision of ICD coding. It outlines the recommended system for defining cancer. The classification of the oral cancer sites/subsites is more systematic (Moore et al., 2000b). The difference between ICD-9 and ICD-10 is the grouping of the sites of oral cancer where in the latest version, is more specific to the anatomic site.

Furthermore, in ICD-10, neoplasm lies in the codes of C00–D48. The term ‘oral’ includes the lips and all intra-oral sites corresponding to the ICD10 codes C00-C06, where C00 codes lip, excluding the skin of the lip, C01-C02 codes the tongue, C03 codes the gum, C04 codes the floor of mouth and C05 codes palate, while C06 codes other non-specific sites of the mouth which include buccal

mucosa, vestibule mucosa, retromolar area. The ICD-10 excludes sites such as C07-C09 (major/minor salivary glands and tonsil), C10 (oropharynx), C11 (nasopharynx), C12-C13 (sinus and hypopharynx) and C14 (ill defined sites in lip, oral and oropharynx) as 'oral cancer'.

3.2 Epidemiology of oral cancer

3.2.1 Global epidemiology of cancer

In cancer epidemiology, some of the basic definitions to describe populations must be understood. Incidence, prevalence, mortality, and survival are the primary measures for assessing the impact of cancer in population groups. Parkin et al. (2005) stated that *incidence* is the number of new cases occurring, expressed as an absolute number of cases per year or as a rate per 100,000 persons per year. *Prevalence* describes the number of persons alive at a particular point with the disease of interest. *Mortality* is the number of deaths occurring, and the mortality rate is the number of deaths per 100,000 persons per year. The *observed survival rate* is the proportion of persons with cancer who survive for a specified period of time after diagnosis, usually 5 years. This statistic is often presented as a relative survival rate, in which survival from cancer is corrected for the likelihood of dying from other causes (Parkin et al., 2001).

Since 1975, The International Agency Research on Cancer (IARC) has estimated the worldwide incidence, mortality and prevalence of 12-26 cancers including the geographic variation between 20 large 'areas' of the world. The IARC divided the report of worldwide rate of cancer based on developed countries and developing countries. Developed countries comprised of areas in

Northern America, Japan, Eastern Europe, Northern Europe, Southern Europe, Australia and New Zealand. Whereas developing countries comprise of areas in Africa, Caribbean, Central and South America, Eastern Asia: China, other Eastern Asia, South-Eastern Asia, South-Central Asia, Western Asia, Melanesia and Micronesia/Polynesia (Parkin et al., 2005).

In the year 1994, IARC reported a comprehensive survey of 10 countries and geographical regions, 5 of which were in the developing countries (Africa, China, Asia [excluding Japan], Melanesia/Polynesia and Latin America). Data on lung, esophagus, stomach, liver, pancreas, bladder, kidney, oral cavity and laryngeal cancers as well as lymphomas and leukemia were collected and reported as age-standardized, sex specific rates (Pastides, 2001). Of the 7.6 million new cancer cases diagnosed worldwide annually, over half were estimated to be in the developing nations. The overall cancer incidence is 1.8 times higher for males and 1.3 times higher for females in developing nations than in developed nations. In another study stomach cancer was the most common type of cancer among the 11 cancer sites studied in the world, followed closely by lung cancer and then by oral cancer, which is especially prevalent in Asia.

The latest estimation of worldwide cancer was done by Parkin et al. (2005) and Jemal et al. (2007) for USA. Parkin et al. (2005) summarized the global estimation of cancer in the world until the year 2002. They illustrated the estimation of incidence and mortality for 26 cancers in men and women worldwide. The incidence estimation showed that the five most common cancers in males was lung, prostate, stomach, colon/rectum and liver cancer.

Whereas, breast, cervix uteri, colon/rectum, lung and stomach cancer was the five highest incidence of cancer in females (Table 3.1).

Table 3.1 Incidence and Mortality by Sex and Cancer Site Worldwide in year 2002

	INCIDENCE						MORTALITY					
	MALES			FEMALES			MALES			FEMALES		
	Cases	ASR (World)	Cumulative risk (age 0–64)	Cases	ASR (World)	Cumulative risk (age 0–64)	Deaths	ASR (World)	Cumulative risk (age 0–64)	Deaths	ASR (World)	Cumulative risk (age 0–64)
Oral cavity	175,916	6.3	0.4	98,373	3.2	0.2	80,736	2.9	0.2	46,723	1.5	0.1
Nasopharynx	55,796	1.9	0.1	24,247	0.8	0.1	34,913	1.2	0.1	15,419	0.5	0.0
Other pharynx	106,219	3.8	0.3	24,077	0.8	0.1	67,964	2.5	0.2	16,029	0.5	0.0
Esophagus	315,394	11.5	0.6	146,723	4.7	0.3	261,162	9.6	0.5	124,730	3.9	0.2
Stomach	603,419	22	1.2	330,518	10.3	0.5	446,052	16.3	0.8	254,297	7.9	0.4
Colon/rectum	550,465	20.1	0.9	472,687	14.6	0.7	278,446	10.2	0.4	250,532	7.6	0.3
Liver	442,119	15.7	1.0	184,043	5.8	0.3	416,882	14.9	0.9	181,439	5.7	0.3
Pancreas	124,841	4.6	0.2	107,465	3.3	0.1	119,544	4.4	0.2	107,479	3.3	0.1
Larynx	139,230	5.1	0.3	20,011	0.6	0	78,629	2.9	0.2	11,327	0.4	0.0
Lung	965,241	35.5	1.7	386,891	12.1	0.6	848,132	31.2	1.4	330,786	10.3	0.5
Melanoma of skin	79,043	2.8	0.2	81,134	2.6	0.2	21,952	0.8	0.0	18,829	0.6	0.0
Kaposi sarcoma*												
Breast				1,151,298	37.4	2.6				410,712	13.2	0.9
Cervix uteri				493,243	16.2	1.3				273,505	9.0	0.7
Corpus uteri				198,783	6.5	0.4				50,327	1.6	0.1
Ovary				204,499	6.6	0.5				124,860	4.0	0.2
Prostate	679,023	25.3	0.8				221,002	8.2	0.1			
Testis	48,613	1.5	0.1				8,878	0.3	0.0			
Kidney	129,223	4.7	0.3	79,257	2.5	0.1	62,696	2.3	0.1	39,199	1.2	0.1
Bladder	273,858	10.1	0.4	82,699	2.5	0.1	108,310	4.0	0.1	36,699	1.1	0.0
Brain, nervous system	108,221	3.7	0.2	81,264	2.6	0.2	80,034	2.8	0.2	61,616	2.0	0.1
Thyroid	37,424	1.3	0.1	103,589	3.3	0.2	11,297	0.4	0.0	24,078	0.8	0.0
Non-Hodgkin lymphoma	175,123	6.1	0.3	125,448	3.9	0.2	98,865	3.5	0.2	72,955	2.3	0.1
Hodgkin disease	38,218	1.2	0.1	24,111	0.8	0.1	14,460	0.5	0.0	8,352	0.3	0.0
Multiple myeloma	46,512	1.7	0.1	39,192	1.2	0.1	32,696	1.2	0.1	29,839	0.9	0.0
Leukemia	171,037	5.9	0.3	129,485	4.1	0.2	125,142	4.3	0.2	97,364	3.1	0.2
All sites but skin	5,801,839	209.6	10.3	5,060,657	161.5	9.5	3,795,991	137.7	6.4	2,927,896	92.1	4.9

(Parkin et al., 2005).

Besides that, Figure 3.1 also showed the ranking of cancers for men and women as number of new cases, together with the corresponding numbers of deaths in the developing and developed regions of the world. In men, although lung cancer is the most common cancer worldwide, it is in second place behind cancers of the prostate in developed countries. In women, cervical cancer is the second in importance in developing countries, but is the seventh in the developed world, with fewer cases (83,000) than for cancer of the corpus uteri (136,000) and ovary (97,000).

In term of estimation of newly diagnosed cancer in USA, the overall estimate is about 1.44 million new cancer cases, and about 22,560 (1.6%) cases of oral

cancer in both sexes are expected to be newly diagnosed in 2007 (Jemal et al., 2007).

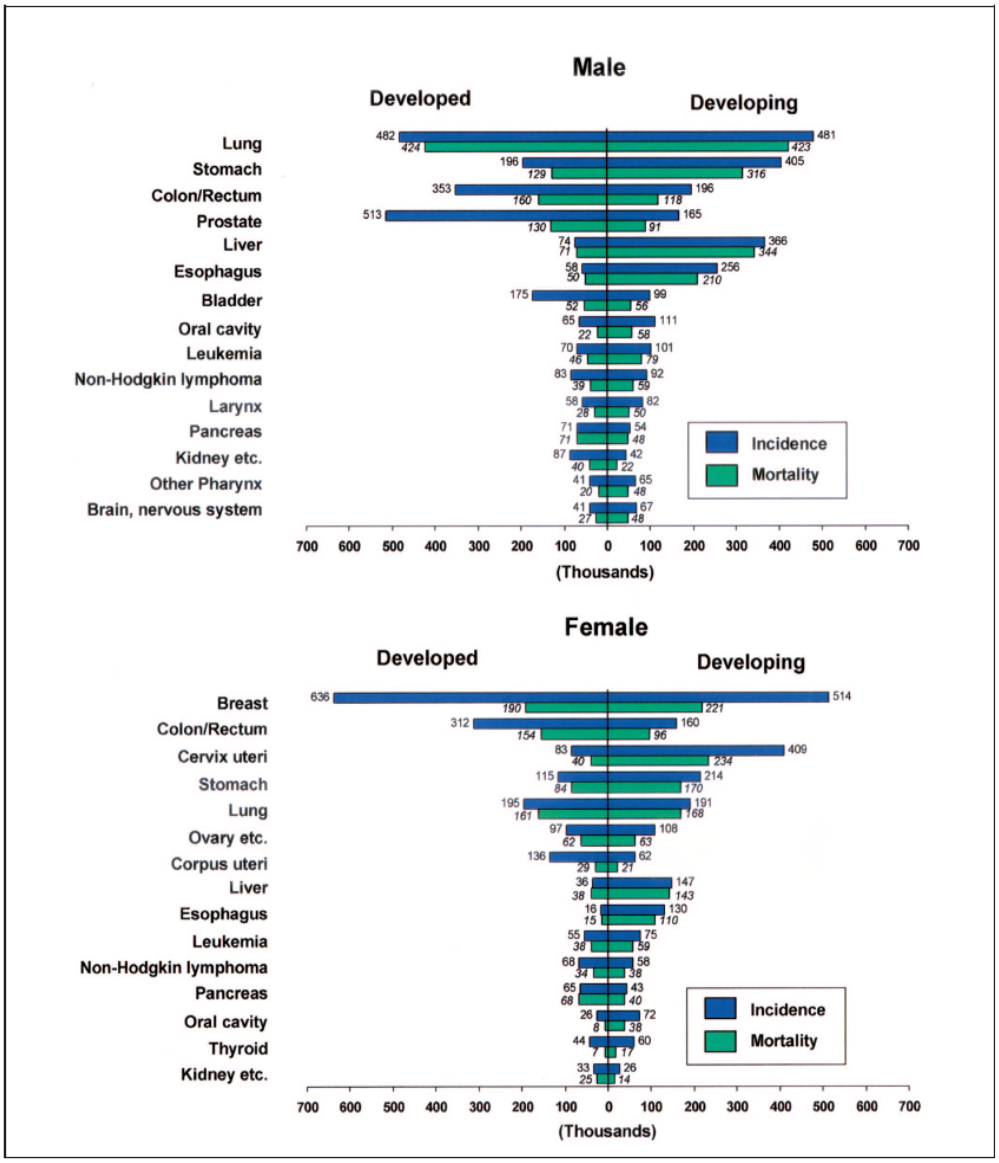

Figure 3.1 Estimated Numbers of New Cancer Cases (Incidence) and Deaths (Mortality) in 2002. Data shown in thousands for developing and developed countries by cancer site and sex (Parkin et al., 2005).

Prostate cancer (218.890 cases) is the highest new cancer cases estimated in USA among men, and breast cancer among women (178.480 cases). Oral and pharynx cancer is one of the top ten cancers among men in USA (ranked ninth).

3.2.2 Incidence of oral cancer in the world

In 1998 oral cancer was ranked as one of the top ten cancers worldwide, with broad differences in geographic distribution (Rodrigues et al.,1998). In developed countries, oral cancer is less common but it is the eighth most common form of cancer overall.

In 2005, Parkin et al. reported on the estimation of global cancer statistic in year 2002 in five continents. The findings showed that in terms of number of cases, oral cancer incidence is the 11th most common cancer in the world (Parkin et al., 2005). Based on sex distribution, oral cancer ranked 8th for male and 13th for females. Cancers of the oral cavity accounted for 274,289 new cases in 2002, with almost two-third of them in men. The highest incidence among males is reported in Bas-Rhin, Northern France and Caldavos due to the high consumption of crudely distilled spirit, with annual rates of 49.4 per 100.000, while the highest rates among females occur in India which is associated with the habit of betel quid chewing in addition to smokeless and smoked tobacco (Stewart and Kleihues, 2003; Reichart, 2001). The next highest incidence in men and women is in Melanesia (ASR 31.5 per 100,000 in men and 20.2 per 100,000 in women), followed by Western Europe (11.3 per 100,000), Southern Europe (9.2 per 100,000), South Asia (12.7 per 100,000), Southern Africa (11.1 per 100,000), and Australia/New Zealand (10.2 per 100,000) for men. After Melanesia, the incidence rate for women is relatively high in Southern Asia (8.3 per 100,000) (Parkin et al., 2005).

3.2.3 Incidence of oral cancer in developed countries

In the United Kingdom (UK), there were approximately 2000 newly diagnosed cases of oral cancer each year, with ASR 4.5 per 100,000 in 1994 as reported by IARC (2003). This represents 1-2% of the total cancer incidence. (Stewart and Kleihues, 2003b)

In the United States of America (USA), cancer of the oral cavity and pharynx accounts for 3% of all cancers (Canto and Devesa, 2002). The incidence and mortality of oral and pharyngeal cancers were estimated to be 36,100 new cases and 7,800 deaths per year. The age-adjusted rate for total oral cavity and pharynx cancers was 8.3 per 100,000 population in 1994–1998, but varies greatly (range 4.8 to 17.7 per 100,000) according to race and sex groups. In the year 2006, the estimated new oral and pharyngeal cancer cases in USA shows a slight decrease which are 32,040 new cases (23,360 cases for men and 8,680 cases for women) and 7,430 deaths (Jemal et al, 2006). In addition, oral cancer is one of the several cancers that occur more frequently in Blacks than Whites in USA, ranking 6th among Blacks and 11th among Whites (Day et al. 1993).

Oral and or pharyngeal cancer incidence and mortality rates in other countries have been stable in some countries or increased in others in the last four decades. Sharp increases in incidence have been reported in Germany, Denmark, Scotland, Central and Eastern Europe, and there are also increases in Japan, Australia and New Zealand, and in the USA among non-whites (Stewart and Kleihues, 2003).

3.2.3 Incidence of oral cancer in developing countries

In developing countries, it has been apparent for decades that the global picture is dominated by the incidence of oral cancer in Southern Asia and oral cavity plus nasopharyngeal cancer in South-East Asia. More than 100,000 cases of oral cancer occur every year in South and South-East Asia, with poor prospect of survival. In certain countries such as Sri Lanka, India, Pakistan and Bangladesh, oral cancer is the most common and accounts for about one-third of all cancers. In parts of India, oral cancer represents more than 50% of all cancers (Stewart and Kleihues, 2003). For instance, in Trivandrum, Kerala, India, the oral cavity is the most common site of cancer for men and the third most common site of cancer for women (Hashibe et al., 2000).

In year 1974, the average annual incidence rate of oral cancer (1963–1972) in Myanmar was 363 per 100,000 populations. The tongue was the most common oral site, constituting 31.2% of all oral cancers, followed by the gingiva, alveolar process (gum) and the floor of the mouth (19.8%), cheek (16.3%), tonsil and faucial pillars (19.8%), and lip (2.8%). However, even though for the last 28 years (1974-2001), oral and oropharyngeal cancers have consistently been the fifth most common cancers for both sexes, the most common site of oral cancer was found to be different. The gum and floor of the mouth (41.9%) for that period has been the most common site, followed by lip (25.3%), tongue (19.8%), and oropharynx (13.0%) (Way et al., 1984). Reichart and Way (2006) attributed the heavy betel quid chewing with tobacco habit as the cause of oral cancer in this population.

In Thailand, oral cancer has been reported to be also common. In 1988—1991, oral cancer frequency was about 3.5% of all cancers, ranking fifth for both sexes with an age standardized incidence rate (ASR) of 5.2 per 100,000 for males and 4.8 per 100,000 for females (Reichart et al., 2003). However, the prevalence of oral cancer appears to be on the decrease because the traditional oral habits such as betel quid chewing and smoking of traditional cigars have largely been given up by many Thais (Reichart et al., 1990; Reichart et al.,1995: Reichart et al., 2003).

Malaysia, the nearest country to Indonesia has some similarities in ethnic composition (Malay) and diet. The Malaysian National Cancer Registry (NCR) in year 2003 reported that the incidence of gum, floor the mouth, palate and other non-specific sites of mouth (ICD 10 C03-C06) in Peninsular Malaysia was ranked 19th and 16th most common types of cancer among males and females respectively. However this incidence does not include the incidence of lip and tongue (ICD 10 C00-C01) cancers (Lim et al., 2004). This figure may seem low as compared to the world incidence. However, when all these sites were combined, the recalculated ASR for oral cancer in Malaysia was higher at i.e. 3.7 per 100,000 for males and 4.7 per 100,000 for females. It was also observed that gum, floor of the mouth, palate and other parts of mouth cancer incidence are highest among ethnic Indians. The NCR in year 2004 also reported that for year 2003, mouth cancer was ranked 6th and 3rd most common cancers for Indian males (ASR=7.2) and females (ASR=16.5) respectively while cancer of the tongue was ranked as the 9th most common for Indian males (ASR=6.4) and females (ASR=6.8) (Lim et al., 2004).

In Indonesia, the Indonesian Health Ministry reported 200,000 new cases of cancer each year (Departemen Kesehatan Republik Indonesia, 1999). The Ministry of Health of Indonesia had also reported on cancer incidence based on histopathological data from 13 centers in the year 1999. The most common cancer in Indonesia for males is nasopharyngeal cancer with an ASR of 10.04 per 100,000 and cervical cancer is the most common for females with an ASR 23.95 per 100,000 Oral cancer is ranked 9th for males and 13th for females in comparison to other cancer in Indonesia. The ASR of oral cancer in general was 3.05 per 100,000. The ASR of oral cancer was higher in males (3.61 per 100,000) as compared to females (2.17 per 100,000). Tongue cancer is the most common site amongst males and females, followed by buccal mucosa, gingiva and floor of the mouth. The most affected age group for oral cancer was 55-64 years old (Departemen Kesehatan Republik Indonesia, 1999).

In a study which also utilized hospital-based data from Java Island, a prevalence of oral cancer of 12.7% was reported (Budhy et al., 2001). Another hospital-based study in Yogyakarta, Java Island over a period of 1995 -2002, found that tongue cancer was the most frequent type of oral cancer (47.9%) as compared to other sites (Widiati, 2001). Besides data from Java Island, an audit of histopathology data (1995-2002) in Medan, Sumatera Utara showed that out of a total of 1015 oral lesions, 346 (34.1%) cases were oral cancer (Ginting and Elbritha, 2003**)**.

3.2.5. Oral cancer mortality

The global mortality of oral cavity and pharyngeal cancer was estimated to be 197,000 in the year 1990, in which about 100,000 deaths were caused by cancers

of the 'mouth' (lip and oral cavity) (Pisani et al., 1999). The mortality rate of oral cancer in year 2002 increased to 127,259 cases with ASR of 2.9 per 100,000 for males and 1.5 per 100,000 for females (Parkin et al., 2005).

In 1980, 4.6% of deaths arising from all cancers in Brazilian males were specifically caused by mouth and pharyngeal tumors, compared to the 1.1% of deaths among females. These rates increased in 1995 to 5.2 and 1.3% respectively. Between 1980 and 1995, the age-adjusted mortality rates increased from 2.5 to 2.7 per 100,000 males and from 0.6 to 0.7 per 100,000 females (Filho, 2002).

Mortality rates for oral cancer have also increased substantially in many other countries. In Germany, Czechoslovakia, and Hungary, almost a 10-fold increase in mortality from oral cancer in men aged 35-44 years occurred within one generation. Systematic analyses of cancer mortality data for 28 European countries have shown pronounced upward trends in oral cancer mortality in the group aged 35-64 years from 1955-1989. Inspection of age-specific mortality rates reveals substantial increases at younger ages in most European countries (Parkin et al., 2005).

3.2.6 Gender distribution of oral cancer

The male and female ratio of oral cancer occurrence varies from 2-15:1 depending on the anatomical sub-site, with extreme ratios characteristic of tongue, floor of the mouth and pharyngeal cancer (Johnson et al., 2003a). The highest incidence among males is reported in France, in the east-central part of the country along the German border (called Bas-Rhin) and on the Britany coast

(Caldavos), while the highest rates among females occur in India (Blot et al.,1996). Sex distribution varies considerably in different geographical areas due to varying risk factors (Johnson, 2003b; La Vecchia et al., 1997). In the Western countries, men are affected two to three times as often as women, largely because of their greater indulgence in alcohol and tobacco. However the incidence of oral cancer for women can be greater than or equal to that for men in high-incidence areas such as India, where chewing (and sometimes smoking) are also common amongst women, although this varies considerably from region to region (Johnson, 2003a).

3.2.7 Age distribution of oral cancer

Oral cancer predominantly is a disease found in middle-aged and older persons (Neville and Day, 2002a). The incidence of oral cancer increases with age in all parts of the world. The incidence of oral cancer at any age is comparatively low in western countries (2-6% of all malignancies), but on the Indian sub-continent the rates were as high as 30-40% (Parkin et al., 1993). However, in the past two to three decades, there has been an alarming increase in oral cancer especially among younger men in many Western countries (Johnson, 2003a) and Indian sub-continent (Gupta, 1999a; Gupta and Nandakumar, 1999b). In the West such as UK and France, 98 % of oral and pharyngeal cases are in patients over 40 years of age. Studies from UK have reported rising trends in oral cancer particularly for tongue cancer among young adults (Johnson and Warnakulasuriya 1993a). Significant increases in incidence and mortality amongst younger males have also been reported in England and Wales during the last 30 years (Hindle et al., 1996). This is similarly reported in the USA by Davis and Severson (1987).

In high-prevalence areas such as the Indian subcontinent, cases occur prior to the age of thirty five due to heavy abuse of various forms of tobacco (Johnson, 1991). Furthermore, a number of cases of oral cancer occur in both young and old patients often in the absence of traditional alcohol and tobacco risk factors and may pursue a particularly aggressive course (Johnson, 2001). In Sri Lanka nearly 5% of oral cancer is diagnosed in young patients (Siriwardena et al., 2006). In India, oral cancer is reported to be reaching epidemic proportions in the younger population (under 40 years of age) due to the increasing use of areca products which cause oral submucous fibrosis, a potentially malignant oral condition (Gupta et al., 1999a; Warnakulasuriya, 2001). Between 16 – 28% of all oral cancer patients seen at various institutions in India were estimated to have used areca products (Gupta et al., 1999b). A survey of young cancer patients carried out in UK by Mackenzie et al. (2000) reported that most were exposed to traditional risk factors of tobacco smoking, drinking alcohol and low consumption of food and vegetables. Furthermore, a comprehensive literature review of risk factors for oral cancer in young people undertaken by Llewellyn et al. (2001) showed that most studies suggest that 4-6% of oral cancer now occur at ages younger than 40 years. Information on many aspects of etiology for this disease in the young implicating occupational, familial risk, immune deficits and virus infections are meager. Besides, genetic instability has also been hypothesized as a likely cause (Llewellyn et al., 2001).

3.2.8 Ethnic distribution of oral cancer

Ethnicity also strongly influences prevalence as a result of social and cultural practices, as well as influencing death rates owing to socioeconomic differences. Ethnicity is defined as one in which individuals themselves define the group to

which they belong, as a result of cultural habit or beliefs, together with other factors such as language, religion, and diet which may affect health (Scully and Bedi, 2000).

At present, no clear trend has been observed between the incidence of oral cancer and socioeconomic status (Scully and Bedi, 2000). However, there is growing evidence of intra-country ethnic differences; for example, Asian American (Chinese, Filipino, Vietnamese, Koreans, and Japanese) in California is the major US racial/ethnic group for which the annual number of deaths from cancer exceeds that for heart disease (Jemal et al., 2007). Besides that there was also a significantly higher number of deaths from oral cancer recorded in men from the Indian subcontinent in the UK, than in the indigenous UK population (Balarajan et al., 1984). In addition, oral cancer appears to be most prevalent in areas with a high Asian population (Warnakulasuriya et al., 1996). Similarly, among Indians living in Malaysia, the overall incidence of mouth cancer has long been considerably higher than that among Malay or Chinese subjects and this was confirmed by National Cancer Report 2004. In Australia, migrants from the Mediterranean littoral and the Middle East have lower rates of mouth cancer than the Australian-born population (McCredie et al., 1994). Southeast Asian migrants to France have also been found to have a lower risk of mouth cancer (Bouchardy et al., 1994) as have Maghrebian (Algerian, Tunisian, and Moroccan) migrants (Bouchardy et al., 1996).

3.3 Clinical and Pathologic Characteristics of Oral Cancer and Precancer

Single ulcers, lumps, red patches, or white patches (particularly if they persist more than 3 week) may be manifestations of malignancy (Scully, 2003).

3.3.1 Clinical Presentation of Oral Cancer

Oral cancer has a varied clinical presentation. They may appear as white, red, ulcerated, exophytic, lumps, fissures or a combination of these features (Zain et al. 2002).

3.3.1.1 White lesions

Oral cancer/carcinoma may develop in a white area but is indurated. The surface of lesion may be nodular or ulcerated. There may be fixation if the lesion occurs on a movable part of the mucosa. It may also present as a fungating mass (Neville et al., 2002b). The clinical features for oral cancer maybe similar to those described for premalignant or potentially malignant lesions for example oral leukoplakia. The clinical presentation of oral leukoplakia will be described further under potentially malignant lesions.

3.3.1.2 Red lesions

Oral cancer may develop in a red area but there is induration where the tissue feels firm and thickened throughout the lesion or at the margins if ulcerated (Neville and Day, 2002a; Neville et al., 2002b). The clinical features may be similar to erythroplakia which will be described under potential malignant lesion.

3.3.1.3 Ulcerated lesions

In the ulcerated form, oral cancer feels hard (indurated) on palpation of the margins. The growth pattern is characterized by a depressed, irregularly shaped, ulcerated, central area with a surrounding “rolled”

border of normal, red or white mucosa. The rolled border results from invasion of the tumor downward and laterally under adjacent epithelium (Neville et al., 2002b).

3.3.1.4 Exophytic lesions

An exophytic lesion typically has a surface that is irregular, fungating, papillary, or verruciform, and its color may vary from normal to red to white, depending on the amount of keratin and vascularity (Neville et al., 2002b).

3.3.2 Clinical and Pathologic Characteristics of Precancers (Potentially malignant lesions/conditions)

Oral cancer may arise in apparently normal mucosa, but many are preceded by clinically obvious premalignant lesions, especially erythroplakia (red patch), leukoplakia (white patch), a speckled leukoplakia (red and white), or verrucous leukoplakia, and many others are associated with such lesions (Scully, 2003; Pindborg et al., 1997).

The term oral precancer and oral premalignancy signify an invariable development of cancer from these lesions. However not all precancers or premalignant lesions develop into cancer, thus the terms “potentially malignant oral lesions and conditions’ were proposed (Johnson, 1993b). The potentially malignant oral lesions include leukoplakia and erythroplakia of various clinical presentations and mixed lesions (Paterson, et al. 1996; Scully, et al. 2003). The potentially malignant oral conditions include sideropenic dysphagia, erosive lichen planus, oral

submucous fibrosis, tertiary syphilis, discoid lupus erythematosis, and actinic keratosis (Johnson, 2003a). In view of the wide spread usage of the terms precancerous, premalignant, precursor lesions and potentially malignant lesions in the literature, these terminologies will be used synonymously in this review.

A panel of experts in WHO had published the histological typing of cancer and precancer of the oral mucosa to update the classification of oral cancer and precancer (Pindborg et al, 1997). They classified the precancers of the oral mucosa as precancerous lesions and conditions, based on the clinical characteristic as well as histopathological characteristics.

A precancerous lesion was defined as a morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart (Pindborg et al., 1997). The clinical classification of precancer includes: leukoplakia and its clinical variants, erythroplakia and palatal keratosis associated with reverse smoking. The histopathological characteristics of precancers include: squamous epithelial dysplasia, squamous cell carcinoma in situ and solar keratosis.

A precancerous condition was defined as a generalized state associated with significantly increased risk of cancer. These include sideropenic dysphagia, lichen planus, oral submucous fibrosis, syphilis, discoid lupus erythematosus, xeroderma pigmentosum and epidermolysis bullosa (Pindborg et al, 1997).

3.3.2.1 Leukoplakia

The term leukoplakia is used irrespective of the presence or absence of epithelial dysplasia. Leukoplakia is a clinical term for a persistent adherent white patch with no histological connotation and no implied premalignant potential (Pindborg et al., 1997).

Similar to the definitions of oral precancerous lesions and conditions, the term leukoplakia and its clinical variants have undergone many changes over time (Kramer et al., 1978; Axell et al., 1984). The currently accepted definitions of leukoplakia are that it is ‘a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion (Pindborg et al, 1997).

Leukoplakia is unusual in patients under 30 years of age and is usually encountered in the fifth through seventh decade of life. Generally, leukoplakia is more common in men than women; however the reported male/female ratios may vary considerably. The prevalence of oral leukoplakia demonstrates geographic differences and ranges from 0.4 to 11.7% (Muller, 2007). The wide variation noted is most likely due to cultural differences in diet, tobacco smoking, betel quid use/ chewing of tobacco and alcohol (Reichart, 2001). Another reason for the wide disparity could be how leukoplakia was defined in earlier studies, and may include frictional keratosis and nicotine stomatitis (Muller, 2007).

3.3.2.2 Erythroplakia

In the second edition of the 'Histological typing of cancer and precancer of the oral mucosa', erythroplakia was defined as "fiery red patch that cannot be characterized clinically or pathologically as any other definable lesion''. This definition is now widely accepted and similar to leukoplakia, it is based on the principle of diagnosis by exclusion (Pindborg et al., 1997). Erythroplakia lesions are velvety red plaques that in at least 85% of cases show frank malignancy or severe dysplasia.

3.3.2.3 Malignant Potential of Precancers and Other lesions/ conditions

In contrast to erythroplakia most white lesions do not have a high potential where the extent of possible malignant change is dependent on the type of leukoplakia. Speckled or verrucous leukoplakias are more likely to be potentially malignant. Carcinomas are seen 17 times more frequently in erythroplakia than in leukoplakia, but leukoplakias are far more common. The prevalence of malignant transformation in leukoplakia ranges from 3-33% over 10 years (Johnson, 2003a).

In another study, the risk of multiple carcinomas was five times greater in patients with oral cancer preceded by leukoplakia than those who had no precancer lesions (Scully et al, 2003). The overall incidence of cancer development ranging from 4.4 to 31.4% or to as high as 36% when moderate or severe dysplasia is present have been reported (Lind, 1987; Lee et al, 2000; Silverman et al, 1984).

Besides potentially malignant lesion which may develop to oral cancer, there are also some conditions which may also change into cancer, and it is called oral precancerous condition. The lesions include oral submucous fibrosis and oral lichen planus (Muller, 2007).

Oral submucous fibrosis is a chronic, irreversible disease that usually involves buccal mucosa, but may affect the entire oral cavity as well as oropharynx. It usually starts as a complaint of burning sensation while eating spicy foods, followed by blanching, hardening of mucosa and the presence of fibrous bands with limited mouth opening. In one study, a 7.6% malignant transformation rate was observed for oral submucous fibrosis over a 17-year period (Murti et al., 1985). Oral submucous fibrosis is strongly related to the areca nut chewing.

Another premalignant condition is oral lichen planus. Oral lichen planus is also a chronic disease which clinically is characterized by white striae and histologically characterized by a subepithelial band of lymphocytes and liquefaction degeneration of the basal cells. Clinically, lichen planus may be divided into non erosive, erosive, and plaque type, where the two latter types are difficult to distinguish from leukoplakia or erythroplakia (van der Waal et al., 1997). The relationship between oral lichen planus and oral squamous cell carcinoma is controversial. When a strict criterion is applied, there is only a less than 2% potential for a malignant change (van der Waal et al., 1997).

3.3.3 Histopathology of oral cancer

More than 90% of oral cancer is Squamous Cell Carcinoma (SCC) (Johnson, 2005). SCC is 'a malignant epithelial neoplasm exhibiting squamous differentiations as characterized by the formation of keratin and/or the presence of intercellular bridges'. It has been customary to grade these neoplasms in an attempt to predict their aggressiveness and hence to establish a prognosis for a patient or an indicator for the most effective treatment. The grades are described by Pindborg et al, (1997) as below:

Grade 1: Well differentiated: Histological and cytological features closely resemble those of the squamous epithelial lining of the mucosa. There are varying proportions of basal and squamous cells with intercellular bridges: keratinization is a prominent feature: few mitotic figures are seen and atypical mitosis or multinucleated epithelial cells are extremely rare: nuclear and cellular pleomorphism is minimal.

Grade 2: Moderately differentiated, this is a neoplasm with features intermediate between well differentiated and poorly differentiated. Compared with well-differentiated squamous cell carcinomas, these have less keratinization and more nuclear and cellular pleomorphism: there are more mitotic figures and some are abnormal in form; intercellular bridges are less conspicuous.

Grade 3: Poorly differentiated: Histologically and cytologically there is only a slight resemblance to the normal stratified squamous epithelium of the oral mucosa. Keratinization is rarely present and intercellular bridges

are extremely scarce: mitotic activity is frequent and atypical mitoses can readily be found: cellular and nuclear pleomorphisms are obvious and multinucleated cells may be frequent.

Grade 4: Undifferentiated Carcinoma: A carcinoma that lacks evidence of squamous, glandular or other types of differentiation (Pindborg et al., 1997). Histologically and cytologically generally show a haphazard arrangement, bear little resemblance to the cell origin, tend to vary in size, shape and nuclear configuration, and show frequent mitoses often of abnormal type (Govan et al., 1995)

Well and moderately differentiated tumors can be grouped together as low grade and poorly differentiated and undifferentiated tumors as high grade. When a tumor shows different grades of differentiation, the higher grade determines the final categorization (Pindborg, 1997).

3.3.4 Sites of oral cancer

The prevalence and incidence of oral cancer may differ between countries and is also dependent on the site of oral cancer. Different oral cancer sites (ICD 10 C00-C06) may be associated with different lifestyle risk habits. Oral cancer in different sites may also have different behaviors leading to different prognosis.

3.3.4.1 Tongue cancer

Tongue cancer is the most common site (more than 50%) in the United Kingdom (Neville and Day, 2002a; Batsakis, 2003a), followed by the floor of the mouth (Johnson and Warnakulasuriya, 1993a). The incidence

of tongue cancer varies markedly throughout Europe, with the highest incidence rates reported in France (range 3.6 - 8.0 per 100.000), Slovakia (5.1 per 100.000), Switzerland (4.8 per 100.000), Germany (4.1 per 100.000), and Italy (3.8 per 100.000) (Moore, et al., 2000b). In France, the high incidence of tongue cancer has been attributed to high consumption of crudely distilled spirit. Similarly, in USA, tongue and floor of the mouth are the most common oral cancer site due to heavy drinking and smoking (Stewart and Kleihues, 2003b).

A number of studies have shown that the tongue is the most common intraoral site for cancer (Moore et al., 2000b). Chen et al.(1990) found that more than of 40% oral cancer in Connecticut occurred in this location. Hindle and Nally's study in England and Wales (1991) showed over 30% of oral cancer were on the tongue, while Mashberg et al (1989) derived a similar figure (32.6%) in a study from Italy.

Nearly 75% of the oral carcinomas of the tongue arise in the anterior two-thirds of the tongue, 20% occur on anterior lateral or ventral surfaces, and only 4% occur on the dorsum (Batsakis, 2003a; Neville and Day, 2002a). The lateral borders and base of the tongue are the most "cancer prone" areas and along with the floor of the mouth, make up the common intraoral sites for cancer in most populations (Moore et al., 2000b). It has been suggested that this site predilection for intraoral cancer is due to the pooling of carcinogens in saliva in these food channels and reservoirs (Chen et al., 1990) or 'gutter zones' (Johnson and Warnakulasuriya, 1993). Furthermore, two possible reasons are that carcinogens mixed with

saliva constantly pool in these sites and these regions of the mouth are covered by a thinner, non-keratinized mucosa, which provides less protection against carcinogens (Neville and Day, 2002a). Moore et al (2000b) reviewed that the sites most at risk are tongue (ventral and lateral surfaces), floor of mouth, anterior tonsillar pillar and lingual aspect of the retromolar trigone.

The typical carcinoma of the anterior two-thirds of the tongue presents as a painless, indurated ulcer on the lateral border. It is detected earlier than those of the posterior one-third and also tends to be better differentiated. Thus, the posterior one-third is more aggressive with rapid invasion to the cervical nodes (Batsakis, 2003a; Daftary et al., 1992).

Tongue cancer predilection is most common in males and in general the incidence rates increase with age (Chen et al., 1990). The most commonly cited etiological agents and/or risk factors for tongue cancer are tobacco (smoking and chewing habits) and alcohol abuse (IARC 1986, 1988; Sankarayanan, 1990; Hamada et al, 1991; Franceschi et al, 1992; Johnson and Warnakulasuriya, 1993a; Hindle et al., 1996). However, additional causative factors including nutritional deficiencies and viruses have been suggested (Macfarlan et al., 1996). Recent research have also documented the role of genetic factors as being significant (Wong et al., 1996; Todd et al., 1997).

3.3.4.2 Floor of the mouth

Carcinoma of the floor of the mouth is often located in the anterior part, close to or in the midline. It represents 35% of all intra oral cancers in

epidemiology surveys and appears to be increasing in frequency among females. Of all intra oral carcinomas, oral floor lesions are the most likely to arise from a preexisting leukoplakia or erythroplakia (Pindborg et al, 1997; Neville et al, 2002b). The floor of the mouth is the second most common intraoral site for cancer in developed countries (Silverman, 2001; Johnson, 2001). However, distribution differs in developing countries where it is ranked fourth (Gupta and Nandakumar, 1999b). Cancer of the floor of the mouth is more commonly associated with leukoplakia (Neville et al, 2002b).

3.3.4.3 Buccal mucosa and lip

In the buccal mucosa the majority of cancers are located posteriorly. Often the cancer extends into the upper or lower sulcus. (Pindborg, et al, 1997). Carcinomas of the buccal mucosa can also be seen at the commissure or in the retromolar area. Most are ulcerated lumps and some arise from candidal leukoplakias. Cancer of the buccal mucosa is predominantly due to betel quid chewing habit, such as in India and Taiwan (Gupta and Nandakumar, 1999b; Lee, et al., 2006).

Cancers of the lip usually arise in the vermilion border and the lower lip is most commonly affected. Cancers of the labial commisure are usually preceded by nodular leukoplakia, often associated with a Candida infection (Batsakis, 2003). Unlike intraoral cancers, cancers of the lip arise due to tissue changes caused by age and ultraviolet radiation, namely actinic or senile keratosis and elastosis (Silverman, 2001; Stewart and Kleihues, 2003).

3.3.4.4 Gingiva and Palate

Carcinomas of the gingiva and edentulous alveolar ridge may present as an ulceration and resemble inflammatory lesions. They are often associated with leukoplakia. Carcinomas of the alveolus or gingiva mostly are seen in the mandibular premolar and molar regions, usually as a lump (epulis) or ulcer. The underlying alveolar bone is invaded in 50% of cases, even in the absence of radiographic changes, and adjacent teeth may be loose. The incidence of gingiva cancer is increasing consistently with the increasing usage of betel quid chewing among younger adults in Taiwan and India (Lee, et al., 2006; Gupta and Nandakumar, 1999b).

Palatal cancer usually develops as a rather flat swelling that later ulcerates. The tumors show little tendency to grow deeper. Reverse smokers are at high risk for palatal cancer, which usually develops as an ulcer lateral to the midline of the hard palate (Pindborg et al, 1997). Palatal cancers are usually rare and are mostly seen in reverse smokers. It usually develops as an ulcer lateral to the midline of the hard palate. Reverse smoking is commonly practiced in some Southeast Asian, (such as among the population in Phillipine and India) and South American countries (Neville and Day, 2002a; Ortiz et al., 1996). The habit creates a more severe heat-related alteration of the palatal mucosa known as reverse smoker's palate, which has been associated with a significant risk of malignant transformation (Neville and Day, 2002a).

3.4 Carcinogenesis and Risk Factors

3.4.1 Carcinogenesis

Carcinogenesis or oncogenesis or tumorigenesis means development or induction of cancer (Grizzi and Internati, 2006). Cancer results from an accumulation of genetic alteration (Almadori, et al. 2004) in the genes that code for protein that regulates gene expression, cell division, cell differentiation and cell death. It will continuously develop through multistep process involving initiation, promotion and progression.

To enter the first step of carcinogenesis, the agent called initiating agent (most of the known causes of cancer in humans that may affect the gene material directly or indirectly) play a major role to cause permanent mutation. A permanent mutation in a gene (one that is not repaired by the cell's DNA repair mechanisms) is called an initiating event. The stimulation of an initiated cell to divide is called promotion. All cells in the tumor do not have the same characteristics. Therefore, a small tumor will contain cells in various stages of cancer. The diversity of stages is called tumor heterogeneity. In order for the small tumor to grow and cause cancer, additional permanent mutations must accumulate in the tumor cell over time. The development of these mutations is called progression. On rare occasions, sufficient mutations have occurred in some of the cells of a small tumor to allow a localized tumor to grow, invade the circulation, and set up a tumor at a distant site. The formation of a tumor at a distant site is called metastasis (Figure 3.2). The mutations can be inherited in germ cells or acquired through exposure to a wide variety of biological, chemical, and physical agents present in our environment.

The multi-step model of carcinogenesis is widely accepted and requires the step-wise transition from premalignant lesions to the metastatic tumor phenotype. A variety of alterations accumulate to potentiate this transition and gradually increase malignancy (Tsantoulis et al., 2007). A similar progression has been shown to occur in oral cancer (Califano et al., 1996) from benign hyperplasia, to dysplasia, to carcinomain situ and advanced cancer with accompanying genomic alterations.

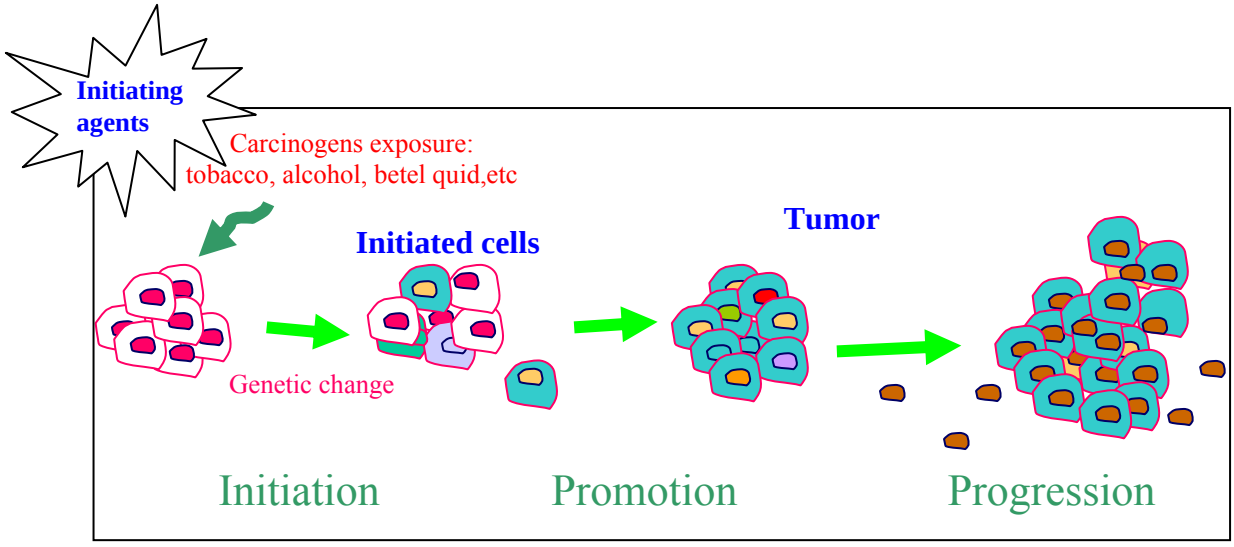

Figure 3.2. Multistep carcinogenesis: initiation, promotion and progression.

Eventhough cancer arises from a sequence of events involving acquired and inherited mutations of the cellular DNA, the genetic susceptibility and promotional factors (e.g. risk factors) may play important role in contributing to carcinogenesis. The carcinogenic potential of an environmental agent may vary depending on the genetic makeup of the host. Thus, some of the genes polymorphism may represent markers of susceptibility of an individual indicating more or less susceptibility to the effects of a particular carcinogens exposure (Nasca, 2001).

The purpose of studies in genetic susceptibility is to identify inherited susceptibility factors. Cumulative evidence indicates that genetic factors contribute to the development of most cancer cases, including those without a clear familial aggregation. Most hereditary cancer syndrome are caused by the mutation or deletion of a single gene, and the inheritance patterns for some of these syndromes often follow the Mendelian transmission models. Because germ-line mutations of major cancer genes are rare in the general population, hereditary cancer syndromes explain only a small fraction of cancer cases in humans. On the other hand, genes polymorphism, although each carries a small relative risk, may contribute to the occurrence of many cancer cases, given their high prevalence in the general population. These genes often interact with environmental agents to increase the risk of cancer (Nasca, 2001).

3.4.2 Risk factors for Oral Cancer

The etiology of oral cancer appears to be multifactorial with smoking and drinking being the major risk factors. Oral cancer is also strongly related to tobacco, betel quid chewing and alcohol abuse and diet although other factors, such as infective agents, may also be implicated (Scully 2000a).

The World Cancer Report in 2003 described the causes of all cancer including oral cancer. It mentioned that tobacco, alcohol drinking and betel quid chewing are still the major risk factors of oral cancer. Diet and nutrition, occupational risk (sunlight), poor oral health (including denture irritation), immune disturbances, infections (HPV, candida albicans) and hereditary influence were also suspected to be involved in cancer development (Stewart and Kleihues, 2003).

An increasing risk of oral cancer due to risk factors have been observed except for syphilis where the risk remained the same as it is treated at an earlier stage by new generations of antibiotic. Currently, the risk factors for oral cancer reported in the literature included tobacco (smoking and smokeless), alcohol drinking, diet and nutrition, viruses, radiation, familial and genetic susceptibility, Candida infections, immunosuppression, the use of mouth wash, syphilis, dental factors, occupational risks and marijuana (La Vecchia et al., 1997; Reichart, 2001; Llewellyn et al., 2001; Johnson 2003b; Stewart and Kleihues, 2003).

3.4.2.1 Tobacco use as a risk factor

On the global scale, the use and abuse of tobacco products is the major cause of oral cancer (Winn, 2001; Johnson, 2001). Smoking is the leading cause of death from cancer, and at least 15% of all cancers are estimated to be attributable to smoking (Parkin et al. 1994). The risk of death associated with cigarette smoking has risen over time as the average duration of smoking has increased. It was estimated that 4.9 million people died of tobacco-related illness in the year 2000, and by 2020s that figure will rise to 10 million deaths per year, and 70% of which will be in developing countries (WHO, 2000a).

Every 10 seconds another person dies somewhere in the world as a result of tobacco use. In developed countries as a whole, tobacco is responsible for 24% of all male deaths and 7% of female deaths, rising to over 40% for men in some of the former socialist countries and 17% for women in the USA. The proportions of cancer deaths attributed to smoking in developing countries as a whole are lower, being about 21% for men and

only 4% for women. However these figures are rising with the fall in global tobacco consumption in the West being matched by growth in developing countries. Indeed, out of the 1100 million smokers in the world, some 800 million are in developing countries, 300 million in China alone, and Indonesia itself is about 100 million. Globally some 3 million deaths a year have been estimated to be attributable to smoking, rising to 10 million a year in 30-40 years time when some 7 million will be in developing countries (Johnson, 2003b). Among men in industrialized countries, smoking is estimated to be the cause of 40-45% of all cancer deaths, 90-95% of lung cancer deaths, over 85% of oral cancer deaths, 75% of chronic obstructive lung disease deaths and 35% of cardiovascular disease deaths in those aged 35-69 years (Johnson, 2003b).

Globally, about 1.1 billion people (one in three adults) smoke today, of which approximately 80% were in countries with low and middle-income. The prevalence of smoking is highest in Eastern Europe and Central Asia and lowest in Middle East and Africa, although this pattern is rapidly changing. The total number of smokers is expected to reach 1.6 billion by 2025, partly as a result of increased trade liberalization and the consequent uptake of smoking in the developing countries, notably in China (Kupper et al. 2002).

In the US some 25% of the population smoke, while in the UK and Australia, the adult smoking rates are currently around 27% and 38% respectively. Many other countries have high rates of smoking, but the

highest reported rates are from China where a national study in 1996 reported that 63% of males were current smokers (Yang et al., 1999). About half of all regular cigarette smokers will eventually be killed prematurely by their habit (Doll et al., 2005).

Smoking is particularly common amongst men where globally it is four times higher than in women. Most smokers start during their teens or early 20s. The reducing of initiation age of smoking throughout the world bring a concern as people who start smoking earlier are less likely to quit and more likely to become heavy smokers (Kupper et al. 2002).

Tobacco is also a major independent risk factor for the development of oral and pharyngeal cancer and other malignancies of the upper aerodigestive tract (Brundtland, 2000). Smoking is estimated to be responsible for about 41% in men of laryngeal and oro/pharyngeal cancer and 15% in women worldwide and these proportions vary amongst different populations (Stewart and Kleihues, 2003b). Oral and pharyngeal cancers have striking geographic and ethnic variations around the globe which is largely dependent on the pattern of tobacco and alcohol use.

Tobacco is usually used in the form of tobacco quid/betel quid, bidi (a local hand–rolled cigarette) smoking and manufactured cigarette smoking. Studies on high consumption of betel quid with or without tobacco reported increased risk of oral cancer. A meta-analysis of 12 case-control studies on bidi smoking (which is very popular in India)

reported an increased risk for oral cancer (OR = 3.1 95% CI 2.0–5.0). The type of tobacco used in manufacturing bidi is speculated to be of major importance in determining the risk of this smoking habit where higher odds ratios were reported for bidi smoking as compared with cigarette smoking. Bidi smoking was also reported to be associated with a significantly higher mortality compared with tobacco chewing (Rahman et al., 2003).

In Southern England significantly raised odds ratios were found amongst young males with oral cancer who had started to smoke before the age of 16 years (OR 14.3; 95% CI: 1.1– 178.8; Llewellyn et al., 2003). In one study, the odds ratio for consumption of more than 20 cigarettes a day was double that of smokers consuming less than 20 cigarettes a day (Hindle et al., 2000a).

In many European and US studies the risks for oral and pharyngeal cancers are similar for cigarette and cigar smokers which is not surprising as the oral cavity is exposed to the carcinogens in smoke whether the smoke is inhaled or not. Furthermore, the overall risk of oral cancer among smokers is 7–10 times higher than for never smokers.

Other habits such as reverse smoking which is strongly associated with palatal lesions also carry a high risk of developing oral cancer. This habit of smoking by holding the burning end of cigarettes or cigars within the oral cavity is reported mainly in parts of India and South America and in the Philippines. In a six-year longitudinal study in Andhra Pradesh in

India among tobacco users with palatal lesions (n = 3196), all new cancers that were detected were found among reverse smokers (Warnakulasuriya et al., 2005). A synergistic effect of hyperthermia acting with tobacco carcinogens resulting in palatal cancers was suggested by Stich et al. (1992).

There is a synergistic effect on oral cancer risk when tobacco and alcohol is used in combination. Heavy smokers (>40 cigarettes/day) and heavy drinkers (30+ drinks per week) have 38 times the risk of developing oral cancer than abstainers from both products (Blot et al., 1988).

3.4.2.1.1. Carcinogenicity of tobacco to oral tissue

The mainstream smoke (the material inhaled by smokers) is an aerosol containing approximately 4,000 specific chemicals and 1010 particles per ml. The particulate matter (tar) contains 3,500 compounds, nicotine (0.1-2.0 mg per cigarette) and also including most of polycyclic aromatic hydrocarbons (Rodgman et al., 2000).

Tobacco smoke contains many carcinogenic combustion products of which polycyclic aromatic hydrocarbons (PAH) are primarily contact carcinogens. These carcinogenic substances include, inter alia, 4-methyl-N-nitrosamines-1-(3-pyridyl)-1-butanone (NNK), numerous polycyclic aromatic hydrocarbons (PAHs) such as benzo(a)pyrene, radioactive polonium and benzene. The carcinogen content varies by type of tobacco product; for instance, black (air-cured) tobacco has a higher content of

tobacco-specific nitrosamines than blond (flue-cured) tobacco, and hand-rolled cigarettes have higher tar content than filter cigarettes.

There are four principal compounds in tobacco called N-nitrosonornicotine (NNN), 4-methyl-N-Nitrosamine-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT), and N-nitrosoanabasine (NAB). These tobacco-specific nitrosamines (TSNAs) are present in very low concentrations in green tobacco, but higher concentrations occur during curing when amine alkaloids in the tobacco leaf react with either nitrite, which is formed by reduction of nitrate by bacterial activity or nitrous oxides, which are combustion by-products of fire-curing. NNN can be formed directly from nicotine (a tertiary amine) or their secondary amine precursor nornicotine while NAT and NAB are formed from their secondary amine precursors anatabine and anabasine, respectively. In contrast, NNK is formed only from nicotine (Bush et al. 2001; Hecht and Hoffmann, 1988).

Nicotine makes up 0.05-4% of the weight of tobacco leaves and smokers extract about 1-2 mg of nicotine per cigarettes (Bergen and Caporaso. 1999). Nicotine is absorbed in seconds throughout the body, and then metabolized to form, principally (80%) cotinine. Nicotine is the constituent of tobacco that is responsible for addiction and the resultant maintenance of smoking behaviour, exerting its addictive effect by activating the brain's mesolimbic dopaminergic reward system (Benowitz, 1992). Individual susceptibility to nicotine addiction varies because it is affected by polymorphisms of genetics that influence dopamine availability (Kupper et al. 2002).

The systemic absorption of nicotine per typical dose may be 3–4 fold greater for smokeless than for smoked tobacco. Even tough the nicotine half life is short “2 hours” the blood nicotine level plateau at high level as it accumulates throughout the day in regular smokeless tobacco users and persists overnight. Both routes give rise to physical and psychological dependency

3.4.2.1.2 Mechanism of Tobacco-related Carcinogenesis

There is no single mechanism of tobacco related carcinogenesis. A variety of tobacco products exits and the methods by which they are consumed influences the release of carcinogens and therefore the link between tobacco use and the cancer causation. Furthermore, the complexity of the mixture of carcinogens in tobacco use might cause different types of damage, and there is also a random component to carcinogenesis (Kupper et al. 2002).

Carcinogens from tobacco products can be taken in directly through inhalation or ingestion (smokeless tobacco) and also may be absorbed into the circulation. Many compounds from tobacco are converted into reactive electrophilic metabolites by oxidative phase I enzymes, to allow the attachment of a conjugate by inactivating phase II enzymes so that the substrates produced in phase I have more potential to damage DNA than the precursor chemicals, that is, the carcinogens in tobacco may become metabolically activated by phase I enzymes (IARC, 1986).

Carcinogens must be metabolically activated to exert their deleterious effect, but this is counteracted by the ongoing detoxification of carcinogens, so that the balance between activation and detoxification determines part of the individual susceptibility to the carcinogenic effect of tobacco (Kupper et al. 2002).

The principal PAH carcinogen from tobacco combustion is benzo(*a*)pyrene, which is activated by P450 isoenzymes (CYP) to the carcinogen metabolite benzo(a)pyrenedihydro dihydroxy epoxide (Schwatz, 2000). Such metabolites react with DNA to form (predominantly) guanosine adducts to be able to be detoxified by glutathione S-transferases (GSTs). If these are not detoxified by (GSTs), it will lead to the accumulation of the free radical (DNA adducts) in the blood stream and tissue resulting in the initiation of carcinogenesis (Schwartz, 2000).

The carcinogenic effect of tobacco is not only from tobacco smoke product. The chewing of tobacco may also result in a local exposure of the oral mucosa to what is called tobacco-specific nitrosamines (TSNA). Unusually high levels of carcinogenic TSNAs (e.g. NNN and NNK) were reported in saliva of oral snuff (toombak) users in the Sudan (Idris, et al., 1992) and tobacco chewers in India. Chewing also releases high amounts of reactive oxygen species (ROS), especially when betel quid is present. Both TSNA and ROS are major genotoxic agents involved in chewing tobacco-associated oral cancer (Bartch. et al., 1999).

The effects of tobacco use, heavy alcohol consumption, and poor diet explain over 90 % of cases of head and neck cancer (Johnson, 2001). Dietary components can modify the role of tobacco in carcinogenesis. High fruit and vegetable intake may protect from the deleterious effects of smoking with respect to lung cancer and gastric cancer. A cross-sectional study of 63 healthy male smokers revealed that blood levels of vitamin E and vitamin C and retinol, ά-tocopherol and ß-carotene were inversely associated with PAH–DNA adducts in circulating mononuclear cells. Hence, fruit and vegetables may protect smokers from cancer by reducing the formation of adducts, perhaps by inhibiting DNA and chromosomal damage by carcinogens and altering expression of metabolic enzymes (Grinberg-Funes, 1994).

3.4.2.1.3 Tobacco products

Many tobacco products exist, and their use varies both geographically and over time. Cigarettes are shreds of tobacco wrapped in paper as compared to cigars, where the shredded tobacco is wrapped in tobacco leaf. Local variants of cigars and cigarettes exist such as bidis (tobacco hand-rolled in the dried leaf of various plants), chuttas (small cigars smoked with the burning end held in the mouth), and they often have very high nicotine and tar content. Tobacco also can be smoked using a pipe. Manufactured cigarettes and hand-rolled cigarettes are most intensively consumed, accounting for over 85% of global tobacco consumption (Kupper et al., 2002). The smoking of tobacco in the form of factory-made cigarettes, cigars and cheroots, and loose tobacco in pipes or rolled into hand-made cigarettes is familiar in many countries.

There is great variation in the tar, nicotine and nitrosamine contents, depending on species, curing, additives and method of combustion (Johnson, 2001; Rodu, 2004). Intensity of exposure to tobacco smoke is determined by smoking device used (cigarettes, cigar, pipe, hookah, etc) and for any method, may be determine by the depth of inhalation. The smoking of black tobacco cigarettes represents a greater risk for most tobacco-related cancers than smoking of blond cigarettes. Filtered and low-tar cigarettes entail a lower risk for most tobacco-related cancers than unfiltered and high-tar cigarettes (Stewart and Kleihues, 2003b).

3.4.2.2 Alcohol drinking as a risk factor

Alcohol has been recognized as an important risk factor for mouth cancer for almost half a century (Wynder & Bross, 1957) and together with tobacco consumption accounts for the large majority of oral cancer in developed countries. Approximately 75% of all oral cancers arise in association with alcohol and tobacco use (La Vecchia et al., 2004; Llewellyn et al., 2004). The risk is strongly related to the dose of alcohol drunk, even in the absence of smoking. In the United Kingdom, oral cancer rates have more than doubled during the past 20 years and have increased elsewhere in Europe and the United States (La Vecchia et al., 2004; Schantz and Yu, 2002). It is estimated that 2.9 million individuals (7% of the adult population in the United Kingdom) are dependent on alcohol. There is convincing evidence that high alcohol intake is related to carcinogenesis, especially to cancers of

the mouth, pharynx, larynx, esophagus, and liver (Gerhauser, 2005).

3.4.2.2.1 Variation of content of alcohol beverages/ drinking frequency and risk of oral cancer

Alcoholic beverages can be grouped into beers (brewed by fermenting malted barley and typically containing 5% alcohol), wines (made by fermenting grape juice or crushed grapes, containing 12% alcohol) or spirits (made by distilling fermented products of variety of cereals, vegetables and fruits, containing 40% alcohol) (Stewart and Kleihues, 2003b). Some studies used the term liquors for spirit. Liquor is divided into hard liquors or dark liquors such as whiskeys, brandy and cognac; and light liquors such as vodka, gin, rum and tequila (Blot et al., 1988).

The increased risk associated with different degrees of alcohol consumption varies for each tumor site and beverage type. The risk of head and neck cancer is 5-10 times higher in heavy drinkers than in abstainers. The carcinogenic effect of alcohol appears to be more potent in the oral cavity, pharynx and oesophagus and less potent in the larynx (Stewart and Kleihues, 2003b). A cohort study from Denmark which included 156 cases of oropharyngeal and esophageal cancer, suggested that a moderate intake of wine is not related to the risk of upper digestive tract cancers. However, a moderate intake of beer or spirits increases the risk (relative risk, RR 5.2, for drinkers of >3 beers and spirits/day) (Gronbaek et al. 1998).

Another cohort study from Hawai based on 92 cases of oropharyngeal, esophageal and laryngeal cancer, in a population of Japanese–American men who consumed mostly beer, reported a similar pattern of increased risk for upper aerodigestive tract cancer for beer, wine and spirits, the RR being around 4 for the highest levels of consumption. A case–control study of oral and pharyngeal cancer conducted in four areas of United States, based on 1,114 cases and a comparable number of population controls, had also shown that the risk of oral and pharyngeal cancer was higher among those consuming dark liquor (i.e. distilled alcoholic beverages) (odds ratio, OR=5.5 for males consuming >4 drinks/day) or beer (OR=4.7) than wine (OR=2.5) (Blot et al, 1988).

Some studies reported that among hard liquors (such as whiskeys, brandy and cognac) may be associated with increased risk compared to light liquors (such as vodka, gin, rum and tequila). Rothman et al (1998) reported a RR of 4.4 for high consumption of dark liquor than for those reporting comparable consumption of light liquor. Conversely, a population-based case–control study from the USA, including over 900 cases and a similar number of controls, reported an OR of 13.2 for the highest level of intake (> 4 drinks/day) of light liquor, and 4.6 for dark liquors (Altieri 2000).

The difficulty of assessing the influence of alcohol in the etiology of oral cancer stems from the fact that firstly; most people who drink heavily also smoke and secondly, there was no accurate (and standardized)

measurement of alcohol intake on each individual for research (Ogden and Wright, 1998).

In the United Kingdom, the term units of alcohol is used, where 1 unit contains approximately 8 g of alcohol (Ogden & Wight, 1998). Furthermore, their safe levels for drinking of alcohol equate to no more than 21 units per week for men and 14 units per week for women, whilst high risk is associated with weekly intake greater than 50 units for men or 35 units for women. In the United States, ounces of alcohol is often used, with one drink being the equivalent of 12 oz of beer, 4 oz of wine, and 1.5 oz of spirits (Day et al., 1993) and high risk has been defined as 7 or more ounces of alcohol per day (Kabat & Wynder, 1989).

The alcohol-related risks for oral and pharyngeal cancer, adjusted for tobacco and other confounding factors has been reported by Franceschi et al. (1990) and they reported that the OR of 8.5 and 10.9 for cancer of the oral cavity and pharynx respectively among men drinking 84 or more glasses of wine per week.

A multicentre case–control study from Spain, included 375 cases and 375 matched controls, reported that drinkers of spirits (mainly brandy and whiskey) were between 2 and 3 times more likely to develop oral or pharyngeal cancer than drinkers of only wine or beer. However, no estimate was given for spirits only, and subjects in the highest level of wine and spirit consumption were likely to drink more than the corresponding category of wine drinkers only (Castellsague et al., 2004).

Some studies have attempted to estimate the effect of specific beverages on upper digestive tract carcinogenesis. Their results indicate that all types of beverages contribute to cancer risk in proportion to their alcoholic content (La Vecchia et al.1997). Higher proportions of drinkers of whisky, beer, or combinations of these, but not of wine only, were found among cases of cancer of the oral cavity and pharynx in a case-control study in New York City.

In a large population based study of oral and pharyngeal cancers conducted in four areas of the U.S.A. (Blot et al., 1988), the trends were strongest for beer and spirits, and persisted after adjustment of one for the other. Conversely, there was little or no excess risk for wine drinkers. It appears, therefore, that the most frequently used alcoholic beverage in each population tended to emerge as the most important determinant of oral cancer. Additionally, the study mentioned above indicated that various types of alcoholic beverages are carcinogenic, and that the differences in the risk estimates of each study are partly or largely due to different levels and/or socio cultural correlates of drinking patterns in various populations (La Vecchia et al., 1997).

3.4.2.2.1 Carcinogenicity of alcohol beverages and possible mechanism of oral cancer

Ethanol and water are the main components of most alcoholic beverages, except for some very sweet liqueurs where the sugar content can be higher than that of the ethanol content (IARC, 1988). The amount of ethanol (in milliliters) per type of alcohol beverage was calculated

according to the following concentrations; beer-6% volume, wine-12% and spirits-46% (Odgen, 2005). Ethanol is present in alcoholic beverages as a consequence of the fermentation of carbohydrate with yeast. Synthetic ethanol manufactured from ethylene for the production of alcoholic beverages would contain impurities (Ogden and Wright, 1998). Ethanol contains major metabolite called acetaldehyde which is carcinogenic in experimental animals (Stewart and Kleihues, 2003b).

Kabat and Wynder (1989) had also noted from their studies that polycyclic aromatic hydrocarbons and nitrosamines are the main carcinogenic agent in alcohol beverages. The polycyclic aromatic hydrocarbons and nitrosamines are also present in tobacco and foodstuffs.

The role of ethanol in alcoholic beverages can be considered to be rather similar to that of nicotine in tobacco, when it comes to causing cancer. Although there is a lack of clear experimental evidence for pure ethanol to be considered a carcinogen (Wright & Ogden, 1998) as the compound does not appear to react with DNA in mammalian tissue (Stewart and Kleihues, 2003b), Kabat & Wynder, (1989) had shown that alcoholic beverages are important in the etiology of oral cancer. Alcohol may possibly act as a solvent, allowing the carcinogens from tobacco to penetrate into the tissues or it may act as a catalyst in metabolically activating tobacco carcinogens. Ethanol consumption enhances liver metabolizing activity in both humans and may therefore activate carcinogenic substances. Furthermore, ethanol may alter intracellular

metabolism of the epithelial cells at the target site. Such impairment of cellular function (such as decreased mitochondrial function and increased DNA alkylation) can be aggravated by the coexistence of nutritional deficiencies including vitamin C, niacin, riboflavin and iron (Blot, 1992; La Vecchia et al. 1997).

Three main enzymes are known to be involved in the metabolism of ethanol: alcohol dehydrogenase (found in the cytoplasm); the microsomal ethanol oxidizing system (MEOS) (located in the endoplasmic reticulum); and catalase (the former being the most important). Most alcohol is metabolized by alcohol dehydrogenase to acetaldehyde, a highly toxic substance suspected to cause the tissue damage attributed to alcohol ingestion (Ogden and Wright, 1998).

Several metabolic abnormalities result from the oxidation of excess alcohol, which include overproduction of lactic and keto acids, retention of uric acid, hyperlipidemia and accumulation of fat in the liver. Thus individual variation in the oxidation of ethanol to acetaldehyde (and in particular the length of time required to catalyse the latter to acetic acid by acetaldehyde dehydrogenase (ALDH)) may help explain in part why alcohol can exert an influence on certain tissues in susceptible patients and not in others. In addition, various ALDH isoenzymes exist throughout the body, e.g. gastrointestinal tract, kidney and lungs which can show genetic variation (Ogden and Wright, 1998). Alcohol dehydrogenase and aldehyde dehydrogenase activity have been demonstrated in the oral cavity. Interestingly, the activity of the aldehyde

dehydrogenase is much less than that of the alcohol dehydogenase. This would suggest that it is possible for the cytotoxic acetaldehyde to accumulate in the oral tissues and may thus be a factor in alcohol related oral disease.

One possible pathway on how of alcohol may affect the oral mucosa is through direct effect on the cell membrane. Ethanol is believed to exert an effect on the phospholipid bilayer of the cell membrane. It is widely thought that an extracellular layer of lipids derived from the membrane-coating granules formed in the granular spinous or intermediate layers acts as the permeability barrier towards water and harmful compounds in the oral cavity. This lipid barrier is situated in the superficial regions of the epithelium. If the oral mucosa is exposed to a solvent such as alcohol which removes some of the lipid content, the mucosa becomes considerably more permeable (Ogden and Wright, 1998). This may help explain why heavy drinkers are at much greater risk of developing oral and oesophageal cancer.

Ethanol has been shown to enhance the penetration of the tobacco carcinogen nitrosonornicotine across the oral mucosa (Squier, 1986). Higher concentrations of alcohol produced less permeability which might have been due to its fixative effects, thus reducing the permeability. Alcohol has also been shown to increase the permeability of the oral mucosa to large molecular weight molecules and to cause oral epithelial atrophy (Howie, 1995). It has been suggested that more dilute ethanol (15%) may be more effective than higher concentrations of ethanol (e.g.

40%) because the latter may act as a chemical fixative (Squier, 1991). Howie et al. (2001) found that 50%, rather than 5% or 40%, ethanol, significantly increased the permeability of porcine oral mucosa to triturated water, as well as facilitated the passage of larger molecules such as albumin. However this was not at the expense of the lipid content, which remained constant at 15%, prompting speculation of molecular rearrangement as the most likely course for increased permeability.

3.4.2.3 Quid chewing as a risk factor

Quid is defined as substance, or mixture of substances placed in the mouth or chewed and remaining in contact with the mucosa, usually containing one or both of the two basic ingredients, tobacco or areca nut, in raw or any manufactured or processed form (Zain et al., 1999).

The quid can be divided into 3 basic categories namely: quid with areca nut (areca nut quid) but without tobacco products; quid with tobacco products but without areca nut (tobacco quid); quid with areca nut as well as tobacco products (areca nut quid) (Zain et al. 1999)

Thus, 'tobacco quid' means any quid with tobacco products but without areca nut regardless of its other contents in the mixtures except for betel leaf where it is further termed 'betel quid' and it is recommended that all products within this betel quid be described. Similarly, 'areca nut quid' and 'areca nut and tobacco quid' when used with betel leaf should also

be termed ‘betel quid’ and all compositions within the betel quid should be described (Zain et al., 1999).

3.4.2.3.1 Tobacco quid/smokeless tobacco

Non combustive use of tobacco, or smokeless tobacco use, comes in the form of chewing tobacco (tobacco quid) and snuff (ground or powdered tobacco, either moist or dry) which is inhaled nasally or placed in the mouth, although nasal use has become rare in industrialized countries. Smokeless tobacco or tobacco quid use is particularly common in South and South-East Asia. In these regions tobacco is usually chewed together with another product, such as areca nut, betel leaf, ash, lime, and cotton or sesame oil and thus termed “betel quid”. The average consumption of non-combustive tobacco in regular users is 10–15 g per day and this is kept in the oral cavity for several hours per day (Kupper et al. 2002).

The tobacco quid is placed into contact with mucous membranes, through which the nicotine is absorbed to provide the pharmacological benefit. The use of various forms of snuff, either loose or packeted in small portions, placed in the oral vestibule, is also common in Scandinavia and the USA. In developing countries, however, tobacco is mostly consumed mixed with other ingredients as summarized in Table 3.2 (modified from Johnson 2003b). Chewing tobacco may have a stronger effect than smoking because of the direct contact of the tobacco carcinogens with the oral epithelium as the chewing tobacco is chewed or kept in the mouth (Metha et al, 1981). The levels of PAHs in unburned tobacco are typically low, however, the tobacco-specific

nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and $N\_$-nitrosonornicotine (NNN), are the most prevalent strong carcinogens in unburned tobacco (IARC, 1985). The levels of NNK and NNN in smokeless tobacco products are hundreds to thousands of times higher than those of carcinogenic nitrosamines in any other consumer product designed for ingestion (Hecht and Hoffmann, 1988).

Table 3.2. Some common forms of oral smokeless tobacco

Habit	Ingredients	Population
Pan/Paan/bettle quid	Areca nut, betel leaf/ inflorescense, slaked lime, catechu, condiments, with or without tobacco. (Betel quid)	Indian subcontinent, South-east Asia, Papua New Guinea, part of South America
Khaini	Tobacco and lime (Tobacco quid)	Bihar (India)
Mishri	Burned tobacco (Tobacco quid)	Maharashtra (India)
Zarda	Boiled tobacco (Tobacco quid)	India and Arab countries
Gadakhu	Tobacco and molasses (Tobacco quid)	Central India
Mawa	Tobacco, lime and areca (Areca and Tobacco quid)	Bhavnagar (India)
Nass	Tobacco, ash, cotton or sesame oil (Tobacco quid)	Central Asia, Iran, Afghanistan, Pakistan
Naswar/niswar	Tobacco, lime, indigo, cardamom, oil, menthol, etc (Tobacco quid)	Central Asia, Iran, Afghanistan, Pakistan
Shammah	Tobacco,ash and lime (Tobacco quid)	Saudi Arabia
Toombak	Tobacco, and sodium bicarbonate (Tobacco quid)	Sudan

(Johnson, 2003b with modification in renaming the quid terminology (in parenthesis) based on Zain et al., 1999)

Betel quid is considered as a specific variety of quid which contains tobacco and/or areca nut together with any type of mixtures which include betel leaf. Betel quid chewing has been a common habit in South and Southeast Asia and the Asia Pacific region for a long time. According to ancient history, betel quid use is socially acceptable among

all sections of society, including women and quite often children (Gupta and Ray, 2004). The habit can be described as the practice of masticating a quid containing the seed of ripe areca nut or whole young areca nut, the leaf of vine piper betel, lime and /or tobacco with other ingredients (Saub, 2001).

In most basic form, betel quid is a combination of betel leaf, areca nut and slaked lime (aqueous calcium hydroxide paste), and in some countries tobacco is used in conjunction with the betel quid (Gupta and Ray, 2004). Areca nut in the betel quid may be cured or sun-dried, and chopped, usually placed on a leaf of the piper betel vine (in most parts of the world where the habit is indigenous: importantly, this includes emigrant communities), while the inflorescence is used by some, for example, in Papua New Guinea and Taiwan. Slaked lime may lower pH and accelerates release of alkaloids from both the tobacco and areca nut, with enhanced pharmacological effect. The lime is prepared by baking limestone where available: near coasts this is more often from sea shells or snail shells (such as in Kerala and Sri Lanka) or from coral (as in the Pacific Islands). The chewing of areca nut in various forms and mixtures is deeply embedded in the social and cultural history of India, Sri Lanka, Pakistan, Bangladesh, Myanmar, Thailand, Cambodia, Malaysia, Singapore, Indonesia, Philippines, New Guinea, Taiwan, and China and in emigrant communities therefrom (Johnson, 2003b).

3.4.2.3.2 Geographic distribution and variation of betel quid

The betel quid habit is practiced across class, sex and age. However this situation has changed, where in most parts of Southeast Asia, the habit of betel quid chewing is slowly disappearing and is practiced only by the older generation. However, in Taiwan, the younger generation has picked up this habit due to wide marketing of the commercial product (Lu et al., 1993). A study among Cambodian women refugees in San Diego by Pickwell et al., (1994) had shown that the main reason for chewing betel quid seems to lie in the social affability produced by sharing a quid with friends where offering a quid to someone is a mark of hospitality. Some also believed that chewing betel quid is beneficial for health such as dental health and allows for a better digestion of food if it is consumed after a meal.

In Papua New Guinea, betel quid chewers apply the lime separately with a spatula at the commissure of the mouth (Gupta and Ray, 2004). The hill tribes of Thailand, Cambodia, Myanmar and Laos include cloves, cinnamon and the roots of certain local plants in their betel quid (Reichart,1995). In Taiwan green unripe areca nut of the size of an olive is often used with betel inflorescence or betel leaves. In Cambodia, most users add tobacco to their quid, while others use it to rub the gum or clean the teeth after chewing betel quid and most common users are elderly women (Reichart et al., 1996).

In Malaysia the habit of betel quid chewing is commonly found among certain ethnic groups, namely the indigenous people of Sabah and Sarawak (Zain et al., 1997) and the Indians. The ethnic Indians incorporate tobacco in betel quid, but Malays do not (Shresta et al., 1997).

In India, the composition of betel quid used is almost the same as Indonesian betel quid, but they only use ripe areca nut, usually after curing (generally by roasting or boiling in water). Besides that betel quid can be prepared plain (or astringent) or sweet. Sometimes cardamom and often tobacco are added to the plain variety. In the sweet variety, cardamom, cloves, coconut, sugar crystals, camphor, amber, nutmeg, mace and even coloring agents are commonly added (Gupta and Ray, 2004).

The betel quid consumed in India and many other Southeast Asia countries mostly contain tobacco. Hence, it has been difficult to establish the individual risk effect from the areca nut only. Previously, the role of areca nut alone without tobacco as an oral carcinogen is still unclear in men. Evidence from elsewhere in the world is conflicting. In Guam, where areca nut is chewed alone or with leaf only, there is apparently no increase in oral cancer. Conversely in Taiwan, most heavy chewers of betel quid do not include tobacco, yet it is clearly associated with oral cancer (Ko et. al, 1992). However more current studies in Taiwan where most people consume betel quid without tobacco and without cigarettes smoking found statistically significant association with oral mucosal lesions and oral submucous fibrosis (Yang, et al., 2005).

In Taiwan, an increase in consumption of betel/areca quid chewing habit has been recorded, especially among children and youth. The habit is more common among men (9.8%) than women (1.6%), high among aborigines (42.1%) and starts in childhood (around 12 years) (Chen, et al., 1996; Lu et al. 1993). Increasing betel quid chewing habit among adolescents in Taiwan has also been reported in other studies (Yang et al., 1996). The phenomenon appears to be due to an upsurge in marketing and production of areca nut and the sale of ready-made quid in the shops. Betel quid was more common among boys than girls, and more common among students who smoked, consumed alcohol and had friends who chewed betel quid (Yang et al. 1996).

Other studies done in India also showed that individuals who chewed betel quid with or without tobacco had an increased risk of oral precancers, such as oral leukoplakia (OR=7.0, 95%CI= 5.9–8.3), oral submucous fibrosis (OR=44.1, 95%CI=22.0–88.2),11 erythroplakia (OR=19.8, 95%CI=9.8– 40.0) and multiple oral precancers (OR=37.8, 95%CI=16.2–88.1), after adjustment for smoking and alcohol drinking (Jacob, et al. 2004).

3.4.2.3.3 Betel quid constituents and effect of areca nut

Areca nut is the fourth most common psychoactive substance in the world (after caffeine, alcohol and nicotine), its use extending to several hundred million people. There are several forms of areca nut namely: green unripe, ripe but raw, baked roasted or boiled, fermented, or processed with sweeteners and flavors (Gupta and Ray, 2004).

The quid chewing habits where the quid contained areca nut would result in exposure *inter alia* to areca-nut alkaloids, *N*-nitroso compounds derived from these alkaloids, polyphenols, and when the habit includes tobacco, it also releases tobacco-specific nitrosamines (IARC, 2004). Areca nuts contain potent cholinergic muscarinic alkaloids, notably arecoline, arecaidine and guvacoline, with a wide range of parasympatheticomimetic effects. It promotes salivation and the passage of wind through the gut. It raises blood pressure and pulse rate and elicit degree of euphoria by virtue of their GABA receptor inhibitory properties which contribute to dependence and habituation (Johnson, 2003b). Experimental data documented in IARC monograph 2004, stated that arecoline and arecaidine induces mutation in some cell lines.

The first IARC monograph (1985) on betel quid reported that there was sufficient evidence for carcinogenicity to humans for betel quid containing tobacco (Group 1 carcinogen), but reported inadequate evidence for carcinogenicity to humans for betel quid without tobacco (Group 3 carcinogen). Recently, betel quid without tobacco was classified as a human carcinogen by the International Agency for Research on Cancer in year 2004, as the areca nut was classified as a Group 1 carcinogen, based on its strong association with oral submucous fibrosis, carcinogenicity to animals and plausible mechanisms for carcinogenic action. This is also supported by several case-control studies from India (Sinor et al., 1990; Jacob et al., 2004), Pakistan (Maher et al., 1994) and Taiwan (Lee et al., 2003; Shiu et al., 2000) that

reported betel quid use, specifically without tobacco, is a risk factor for oral cancer and precancer.

3.4.2.4 Genetic susceptibility as risk factors (GSTs and CYP)

Despite the risk of tobacco exposure, alcohol drinking and quid chewing, the majority of patients who smoke or chew tobacco do not get cancer. Factors that influence tobacco-exposed individuals developing malignancy may thus include a combination of exposure and genetic susceptibility (Sreelekha et al, 2001) which may modulate the human genes in metabolizing the risk factors mentioned above. One of the gene that coded enzyme which play a role in metabolizing the carcinogens from tobacco product is called CYP and GSTs. Most chemicals are not biologically active when they enter the body. They need to be converted into biologically active forms before they can interact with host DNA to cause mutation. Cytochrome P450 enzymes act as catalyst in the oxidation process that turns biologically inactive environmental chemicals into substances capable of interacting with DNA. Since Cytochrome P450 enzyme productions under genetic control, individuals vary greatly in their ability to activate various procarcinogens and thus in their risk of developing different forms of cancer (Nasca, 2001). Some evidence suggests that alcohol can activate cytochrome P450 enzyme activity in liver, lung, esophageal, and intestinal tissues, possibly increasing the chance that other carcinogens might be more readily activated (Odgen, 2005).

In addition, the gluthation S-transferase (GST) enzyme system plays an important role in determining an individual's ability to metabolize various carcinogens especially benzo[a]pyrene. Deletion of these genes results in a lack of enzyme activity and reduced elimination of carcinogenic substances. Two of the enzymes, GSTM1 and GSTT1 have been extensively studied in relation to several known carcinogens and their associated DNA adduct, and association of the absence of GST activity with preclinical biological markers (Nasca, 2001).

The purpose of studies in genetic susceptibility is to identify inherited susceptibility factors. Cumulative evidence indicates that genetic factors contribute to the development of most cancer cases, including those without a clear familial aggregation. Most hereditary cancer syndromes are caused by mutation or deletion of single gene, and the inheritance patterns for some of these syndromes often follow Mendelian transmission models with family. Because germ-line mutations of major cancer genes are rare in the general population, hereditary cancer syndromes explain only a small fraction of cancer cases in humans. On the other hand, polymorphism genes, although each carries a relative small risk, may contribute to the occurrence of many cancer cases, given their high prevalence in the general population. These genes often interact with environmental agents to increase the risk of cancer (Nasca, 2001).

Genetic predisposition may also be an important factor in the development of oral squamous cell carcinoma. It is believed that certain

individuals inherit the susceptibility of inability to metabolize carcinogens of pro-carcinogens and/or an impaired ability to repair DNA damage (Scully et al., 2000). A longitudinal study on first-degree relatives of 105 head and neck cancer patients was carried out by Copper et al. (1995). The study showed that 31 of these patients developed cancers of respiratory tract and upper aerodigestive tract. However, population based studies to determine the genetic or familial predispositions to oral cancer are limited by the co-existing risk factors like smoking and alcohol (Johnson et al., 2003b).

Glutathion S-transferase (GST) and Cytochrome P450 (CYP) are the candidate genes for susceptibility in cancer as they catalize the detoxification of many relevant electrophiles and foreign compounds. The metabolism of foreign compounds usually involves two distinct stages, commonly referred to as phase I and phase II. Phase I metabolism involves an initial oxidation of most endogenous chemicals (e.g. hormones and fatty acids) and exogenous chemicals (e.g. PAHs, aromatic amines and mycotoxins) by cytochrome P450 (CYP) monooxygenases. This step is followed by phase II metabolism, which frequently involves detoxifying carcinogenic metabolites catalyzed by gluthathione S-transferases (GST). Then the coordinated expression and regulation of phase I and phase II and their metabolic balance may be important host factors in determining whether exposure to carcinogens results in cancer or not (Sato et al, 1999; Bennett et al., 1999; Sreelekha et al, 2001;).

Gluthathione S-Transferases (GST) family represents a major group of detoxification enzymes. Among the detoxification systems, the GST(s) play critical roles in providing protection against electrophiles and products of oxidative stress (Mannervik and Danielson, 1998; Bennett et al., 1999). GST is also likely to modulate the induction of other enzymes such as quinine reductase, aflatoxin ß1-aldehyde reductase, and glucuronosyl transferase through their ability to metabolize inducing agents. GST catalyze the conjugation of glutathione to electrophilic compounds resulting in glutathione conjugates, which are less reactive and more easily excreted. GSTs are also important for maintaining the cellular genomic integrity and hence, may play an important role in cancer susceptibility (Board et al., 2000). In humans, based on their primary structures, GST have seven families/ classes: ά(alpha), μ(mu), π(pi), θ(tetha), Σ (sigma), Ω(omega), and Φ(zeta) (Mannervik et al., 1985; Mannervik et al., 1992; Meyer et al, 1991). In humans these are located on chromosomes 1,6,11 and 22 (Hayes and Pulford, 1995).

Due to the importance of GSTs in the cellular detoxification of carcinogens, genetic variants of GSTs have attracted the attention of epidemiologist with respect to cancer risk, of which GSTM1 and GSTT1 have been the most commonly studied genes (Board et al., 2000).

The mu class includes at least five genetic variants, and GSTM1 is notable for a “null” allele inactivated by a deletion of DNA coding sequences (Bennett et al., 1999). Loss of GSTM1 enzymatic activity due to the homozygous null genotype occurs in about 50% of white

populations of Europe and north America and Asian (Rebbeck 1997; Hayes and Pufford, 1995). Compared with men, women with the GSTM1 null genotype may have greater risks of tobacco-associated cancers (Bennett et al., 1999).

The theta class of GSTs contains two isoenzymes including GSTT1 and GSTT2, which are located at 22q11.2 and separated by about 50 kb. GSTT1 has an inactivating homozygous deletion polymorphism that occurs in 11%- 18% of whites (Rebbeck, 1997). A functional deficiency of this enzyme activity was associated with increased-risks of smoking associated laryngeal cancer, bladder cancer (Rebbeck, 1997). GSTM and GSTT can both detoxify carcinogenic polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, while GSTP can detoxify smaller reactive hydrocarbons, such as ethylene oxide and diepoxybutane (Pemble et al. 1994). GSTM and GSTT are considered as low-penetrance genes, and usually do not give rise to obvious familial clustering. They may contribute significantly to the number of cancer cases in the general population because of their high prevalence (Zheng, 2001). Individuals with deletions of either GSTM1 locus or GSTT1 locus have no enzymatic functional activity of the respective enzyme and they are known as GSTM1*0 and GSTT1*0 or null allele respectively (Sharma et al., 2006). The absence of the GSTM1 and GSTT1 genes has been reported to increase the risk of several common cancers, particularly those caused by cigarettes smoking such as cancers of the mouth, lung, bladder and breast, in resistance to chemotherapy treatment in drug

response and in disease susceptibility and outcome (Rebbeck, 1997; Hayes and Pulford, 1995).

Polycyclic Aromatic Hydrocarbon (PAH) are present in tobacco smoke and ubiquitous in urban environments. PAH are metabolized to reactive intermediates by polymorphic cytochrome P450 (CYP1A1) and detoxified by phase II enzyme, including glutathione S-transferase (GSTM1) (Wogan, et al., 2004). The CYP1A1 activates tobacco procarcinogens, such as benzo[a]pyrene and aromatic amines into their carcinogenic forms. An A3G base substitution at nucleotide 2455, which is strongly linked to 3801T_C in the 3_-flanking region, encodes for an amino acid replacement of isoleucine by valine at codon 462 and has been reported to be associated with increased enzyme activity (Hashibe, et al., 2003). The variant genotype is suggested to be harmful, possibly by increasing carcinogen activation and generating reactive oxygen species. Moreover, smokers with the CYP1A1 variant genotype may have elevated DNA adduct levels (Hashibe, et al., 2003).

Geographical and ethnic variations exist in genotype frequencies of both GSTs and CYP allele. Some studies showed that polymorphism of CYP1A1 and GSTM1 may increase lung, bladder, and colon cancer risk as well as oral cancer (Wogan et al., 2004; Tanimoto K et al, 1999). It also has been reported that genetic risk for tobacco-related cancer is associated with polymorphism of the CYP1A1 and GSTM1 genes in Japan in terms of genotype frequencies and cigarette smoking dose (Sato et al, 1999; Sato et al., 2000). Besides that, there is a significant 3-fold

increase in risk for patients with premalignant lesion with GSTM1 null genotype (Nair et al, 1999; Buch et al, 2002), and the risk increases further when exposed to environmental toxicants such as chemicals in cigarette smoke, alcohol, betel quid and food such as preservatives (Zheng et al, 1993; Zheng, 2001). The deletion of GSTM1 genes is very common in the general population and is present in about 50% of Caucasians and Asians (Zheng et al, 1993).

3.4.2.5 Diet and Nutrition as risk/protective factors

Recent studies have provided data indicating that dietary factors play an important role in either enhancing or suppressing the risk for oral carcinogenesis. In general, the potential risk for the development of oral cancer due to particular food constituent, concentration of a possible mutagenic or carcinogenic dietary constituent in the food, the preparation of the food and the frequency of ingestion of the food.

It is important to recognize that the cultural habits may also contribute to the development of the oral carcinoma. The cultural habits may influence the types, quantities and combination of foods eaten by a specific ethnic group (Schwartz, 2000). Specifically the reduction in the consumption of vegetables and fruits with a high consumption of salt-preserved meat or fish may contribute to oral cancer development (Schwartz, 2000).

More than 30% of human cancers are probably related to diet and nutrition. The most consistent finding on diet as a determinant of cancer risk is the association between consumption of vegetables and fruit and

reduced risk of several cancers. IARC (2003) reported that about 80% of studies during the last 30 years found a significant protective effect of overall consumption of vegetables and/or fruit, or at least of some types of vegetables and fruit. The European Prospective Investigation into Cancer and Nutrition (EPIC) study found that a daily consumption of 500 g of fruit and vegetables can decrease incidence of cancers of digestive tract by as much as 25% (Stewart and Kleihues, 2003b). Fruit and vegetables may protect against cancer by invoking the interaction of micro-constituent with the processes of carcinogen metabolism, protecting DNA integrity and intercellular communication.

Salted, smoked, pickled and preserved foods (rich in salt, nitrite and preformed N-nitroso compounds) are associated with increased risk of stomach cancer as reported by IARC (2003). Consumption of Chinese-style salted fish has been specifically associated with increased risk of nasopharyngeal cancer in South-East Asia. It is due to partial fermentation and nitrosamine formation (Stewart and Kleihues, 2003b). Studies in these areas have also shown that the dietary habits of communities in China and Uruguay which include continuous consumption of salted meat or fish are relevant to the etiology of oral cancer since it contains nitroso derivatives (De Stefani et al., 1994). Nitrates are oxygen-sensitive and they are reduced during spoilage and become oxidized by nitroso-oxide produced by the oral microflora (Zeng et al., 1992). The derivatives of nitrite such as N-nitrosodimethylamine and N-nitroso-ethylamine also can be found in the salted meat and vegetables in ethnic food (e.g. Asia, South America). These may act as

carcinogen (Zeng et al.,1992; Gao et al,1991). The ingestion of small doses of the nitrite derivatives and alcohol has also resulted in a seven-fold increase in the alkylation damage to DNA in oral mucosal cells (Trickler and Preussmann, 1991). The family of N-nitroso compounds and derivatives in preserved vegetables can be found high in beets, celery, rhubarb, turnip greens, radishes and spinach (Rogers, et al.1995).

Epidemiological studies showed that consumption of red meat (beef, lamb and pork) and processed meat (ham, salami, bacon) more than 80 g per day may increase colorectal cancer risk by 25% and 67% respectively. A hypothesis concerning its potential carcinogenic effect relates to certain compounds that can be formed in meat during cooking, such as heterocyclic amines and polycyclic aromatic hydrocarbons or as a consequence of preserved meat processing (nitrates and nitrites) or endointestinal metabolism (various N-nitroso compounds) (Stewart and Kleihues, 2003b). Studies on carbohydrate intake are difficult because of inconsistent results between studies. The only moderately consistent result seems to be the positive association between consumption of fats of animal origin (except for fish) and risk of colorectal cancer, and olive oil diet which is associated with a reduced risk of cancer (Trichopoulou et al., 2000).

Some additives such as dietary phenolic, have been found from in vitro assay to be both mutagenic and antimutagenic. Food additives are chemicals added to food for the purpose of preservation. Saccharin and it salts have been used as sweeteners for nearly a century. Although some

animal bioassays have revealed an increased incidence of urinary bladder cancer, there is inadequate evidence for carcinogenicity of saccharin in humans (Stewart and Kleihues, 2003b).

Research on vitamins and cancer in humans has focused mainly on carotenoids and vitamin A (retinol), vitamin E, C and some vitamin B (folic acid, B_6). The biological basis for these vitamins is their involvement in either of two metabolic mechanisms commonly called antioxidant effect (carotenoids, vitamin C and E) and methyl donation (folic acid, B_6). Anti-oxidant or chemopreventives such as ascorbic acid (vitamin C), tocopherols (vitamin E) and retinoids (vitamin A) may control the oxidation of nitrates in food and modify their cellular effects (Nasca and Pastides 2001). Low dietary intake of vitamin C has been found to be associated with increased risk of stomach, mouth, pharynx and esophagus cancers (Stewart and Kleihues, 2003b). The largest study on diet and oral and pharyngeal cancer was a population-based case-control investigation conducted in 4 areas of the United States of America (McLaughlin et al. 1988). The findings of this study showed that ß-carotene, vitamin C and fiber content was inversely related with risk of cancer of the oral cavity and pharynx. Other case-control studies conducted in northern Italy by Franceschi et al. (1991) and La Vecchia et al. (1991) found that the strongest protection against oral cancer was also related to frequent fruit consumption, and this was also independent from major potential confounding factors such as tobacco, alcohol and social class correlates.

In fact, the food and food patterns have quantifiable role in oral and pharyngeal cancer risk not only in developing country but also in developed countries which have differences in food type and dietary intake (Franceschi et al., 1999). However, the precise dietary pattern that may entail a reduced oral and pharyngeal cancer risk remains unclear (Franceschi et al., 1999; Levi et al., 1998).

Most of the food groups and dietary pattern studies have been done in western countries. In Asian countries, studies on food and dietary pattern and risk of oral cancer are scarce. So far only three studies have been reported in Asian countries regarding the food and diet pattern in association with oral cancer. The largest study was conducted by Zeng et al. (1993), which is a hospital-based case-control study in Beijing on 404 case/control pairs. Their findings suggested that high intake of proteins (dairy product) are related to decrease risk of oral cancer. At the level of foods and food groups, increased consumption of fresh meat, chicken and liver was significantly associated with a reduction in oral cancer risk. Carbohydrate showed moderately increased risk of oral cancer and finally for dietary fibers, it was consistent with other western studies, that fruit and vegetables showed a strong negative association with oral cancer risk.

Another study in Asia was done by Takezaki et al., 1996. They conducted a case-control study on food and dietary intake of Japanese. They divided the food group into traditional Japanese food and western food and the result showed similar findings for fruit and vegetables.

However, interestingly, they also found that salty food decreased the risk of oral cancer.

Franceschi et al (1999) and Voorips et al. (2000) stated that in conducting the food group and dietary pattern study, the biasness of result can arise when the researcher using the food frequency questionnaires as well as with other methods of dietary assessment, especially if portion sizes have to be estimated. It is due to the lack of past dietary intake recall, method of collecting and analyzing the data (Zeng et al. 1993; Franceschi et al., 1992).

The complexity of human diet presents a challenge to scientists intending to study the relationship between diet and oral cancer. Food may contain chemical compound which are well-known for some, while others are still poorly characterized and seldom can be measured. Based on such background, other researchers introduced a new alternative approach in analyzing the dietary pattern and risk of oral cancer (Marchioni et al. 2005; Marchioni, 2007). This approach is called factor analysis which used the correlation between food and nutrient intake to describe a general dietary pattern which at a later stage may be related to the risk of oral cancer. The factor analysis also values the effect of the diet which is not mediated by one or two specific nutrients, but by nutrients that perhaps operate interactively (Trichopoulos and Lagiou, 2001). A hospital-based case-control has been conducted by De Stefani et al (2005) in Uruguay to find the association of dietary patterns and risk of oral and pharyngeal cancer by using individual food group analysis, factor analysis and determination of empirical scores. The findings

showed similar results and found that the component labeled “stew” loaded by boiled meat, cooked vegetables, potato and sweet potato is positively associated with risk of oral and pharyngeal cancer. The second component labeled “vegetables and fruits” loaded by raw vegetables, citrus fruits, liver, fish and desserts are inversely associated with risk of oral cancer and pharynx. In Uruguay, this analysis is also used in many other type of cancer such as breast cancer (Ronco et al., 2006).

Another study to identify the dietary pattern and risk of oral cancer using factor analysis was conducted in San Paulo, Brazil. The findings showed that consumption in the highest tertile of the ‘traditional’ pattern characterized by rice, pasta, pulses, and meat that are typical of the Brazilian diet showed inverse association with oral cancer (OR 0.51, 95%CI 0.32-0.81) after allowing for alcohol and smoking (Marchioni et al., 2007).

3.4.2.6 Viral, Candida infections and other risk factors

3.4.2.6.1 Virus

a. Human Papilloma Virus (HPV)

The role of viruses, for example Human Papilloma Virus (HPV) and Human herpes Virus (mainly Epstein-Barr Virus) and Herpes Simplex Virus (HSV) have been implicated in oral carcinogenesis (Scully 1993). Viral infections of latent or chronic nature are usually responsible for inducing malignant transformation by interfering with the host’s cell cycle machinery. Certain viruses can become permanent fixtures and integrate their genome in the host’s nucleus, producing factors which cause cellular immortalization. Sometimes, the viruses may produce their

own genes by integrating with host's gene. These viral genes and gene products may affect cell growth and proliferation. Certain viral genes are proto-oncogenes which become oncogenes when inserted into host's DNA and ultimately resulting in malignant transformation (Flaitz and Hicks, 1998).

HPV is recognized as an important and most common virus implicated in cancer of the ano-genital tract, and may also be involved in etiology of cancer of oral cavity and pharynx. Epidemiological and experimental evidence lend some support to this possibility. Increased risk of cancers of the oral cavity and pharynx subsequent to the occurrence of cancer of cervix has been found and suggests common etiological factors, besides smoking (Franceschi et al., 1996; Yeudall et al., 1995).

Certain types of HPV (16, 18, 31, 33, 35, and 39) are associated with oral squamous cell carcinoma and oral premalignant lesions (Johnson, 2003b). The findings in HPV associated with oral cancer showed varying results due to different detection methods. A study in India found high prevalence of HPV (74%) from 91 cases of oral cancer patients with betel quid chewing habit (Balaram et al., 1995). Franceschi et al. (1996) reviewed at least 11 studies on the presence of HPV DNA in cancer of the oral cavity and the controls. Most studies found higher HPV positivity among cases (overall: 106/552, 19%) than controls (overall 32/545, 6%). In addition, this study also found that HPV 16 and 18 seem to be the most frequent types in the oral cavity. Another study has shown that a specific subset of head and neck cancer, oropharyngeal carcinoma

is highly associated with 'high risk' HPV's (Mineta et al., 1998). These findings indicate a stronger etiological link between high risk of HPV infection and group of oral cancer than was previously found. The transmission route of HPV to the oral cavity and oropharynx is still poorly understood. Sexual transmission from the oro-genital tract is conceivable vertical transmission at delivery (implicated with the early onset of recurrent respiratory papillomatosis), digital transmission from periungual infection (known to harbour HPV 16), and transmission from HPV-contaminated fomites are also possible, especially with the presence of macerated or abrated epithelial surfaces (Franceschi et al., 1996).

In contrast, one case control study of oral cancer in men (131 cases and 136 population controls) done by Maden et al. (1992) showed that men with an oral HPV 6 infection had 2.9 times the risk of oral cancer than non-infected ones (95%CI: 1.1-7.3), whereas those with an oral HPV 16 infection did not show any significant association (OR of 6.2, 95%CI: 0.7-52.2). Van Rensburg et al. (1996) in their study of 43 black South African concluded that HPV may not be considered as important in the development of oral cancer. More recently, a large scale multinational, case-control study was carried out by IARC to determine the role of HPV in cancers of oral cavity and oropharynx (Herrero et al., 2003). This study showed that only 3.9% of 766 oral cancers were positive for HPV DNA, which is a relatively low prevalence rate compared to previous studies. However, the prevalence of HPV DNA was higher in cancers of oropharynx with 18.3 of 142 cancers being positive for HPV DNA. HPV

DNA was found to be higher in subjects who either had many sexual partners or practiced oral sex.

b. Ebstein Barr Virus (EBV) and Herpes Simplex Virus (HSV)

Despite the well-established influence of EBV on human B lymphoblasts, the influence of EBV in oral cancer has not been determined. Some studies demonstrated EBV infection in both non-malignant and malignant oral squamous epithelia (Talacko et al., 1991; D'Costa et al., 1998) and thus it has been suspected that an association may exist between EBV and the development of oral SCC. Kobayashi et al. (1999) demonstrated the presence of EBV DNA in seven out of 46 samples of oral SCC. Other studies conducted by Horiuchi et al. (1995) have shown higher frequencies of EBV DNA (24-53%) in oral SCC. Cruz et al. (2000) in their study showed that there is no causal role of EBV in oral carcinogenesis. Thus, further analysis of a larger number of samples is needed to determine whether EBV has a causative role in oral SCC.

Herpes Simplex Virus (HSV) has not been proven to be the direct cause of oral cancer though some studies showed that oral cancer patients have high serum antibody titers to HSV (Johnson et al., 2003b).

3.4.2.6.2 Candida albicans

Candida albicans has been implicated in the pathogenesis of oral premalignant lesions. Superficial fungal hyphae of Candida albicans have been found superimposed on leukoplakia, especially nodular

leukoplakia, some of which had undergone malignant transformation (Rindum et al., 1994). The pathogenesis of Candida invasion whether it is a secondary event or if it causes oral premalignant lesion is still unclear. Candida species are commensals in the oral cavity which become opportunistic during host's immunosuppression due to systemic disease or drug therapy.

3.4.2.6.3 Other factors

Patients who are immunosuppressed after organ transplantation have higher incidence of subsequent cancer development, particularly of the lower lip (De' Visscher et al., 1997). Cases of oral carcinoma of lip in patients with graft-versus-host disease have also been described by Otsubo et al. (1997). The direct role of immunossuppression was not proven in that study and it may be attributed to solar radiation and other risk factors such as smoking. On the other hand, oral squamous cell carcinoma in patients with HIV is rare. HIV infected patients are predisposed to developing Kaposi's sarcoma and lymphomas but not oral squamous cell carcinoma (Walker et al., 2003). As such, oral hairy leukoplakia has never been considered a premalignant lesion (Langford et al., 1995).

One study has mentioned that the use of mouthwash would cause oral cancer, especially for those containing alcohol. However epidemiological evidence demonstrated that the risk of mouthwash causing oral cancer is attributed to the frequency and duration of use and its alcohol content

(Win et al., 2001). There is no cause-effect relationship found between mouthwash and oral cancer in that study.

Occupational risk, such as exposure to excessive solar radiation/ultraviolet light is known to cause lip cancer. UV rays also cause actinic cheilitis which may transform to oral squamous cell carcinomas (Thornhill, 1993). Asbestos, pesticides exposure, burning of fossils fuels have been known to cause cancers of posterior of the mouth, pharynx and larynx (Johnson, 2003b).

One study had shown that individuals with poor oral hygiene are at slightly increased risk for oral cancer (Zheng et al., 1990). These patients with poor oral hygiene often ignored the healthy life-style (inadequate diet, smoking, drinking lack of self-care). The poor dental health hygiene may increase acetaldehyde production from ethanol in saliva in drinkers (Homann et al., 2000).

Tertiary syphilis has been known to predispose to the development of oral cancer along with other risk factors such as tobacco and alcohol (Wynder and Bross, 1957). However, tertiary syphilis is rare in clinical practice and the infection is diagnosed and treated before the onset of tertiary stages (Johnson, 1991).

3.5 The population of Indonesia

3.5.1 Population Characteristics

Indonesia is a huge archipelagic country (Figure 3.3) extending 5,120 kilometers from east to west and 1,760 kilometers from north to south. It encompasses 13,667 islands (some sources say as many as 18,000), with only 6,000 of which are inhabited. There are five main islands (Sumatra, Java, Kalimantan, Sulawesi, and Irian Jaya), two major archipelagos (Nusa Tenggara and the Maluku Islands) and sixty smaller archipelagos. Two of the islands are shared with other nations; Kalimantan (known in the colonial period as Borneo, the world's third largest island) is shared with Malaysia and Brunei, and Irian Jaya shares the island of New Guinea with Papua New Guinea. Indonesia's total land area is 1,919,317 square kilometers.

Figure 3.3 Indonesia Island

Indonesia is the fourth most populous nation in the world after China, India and the United States. According to the estimation for 2005, the current population

of Indonesia is approximately 242 million people. Over two thirds of the population resides in Java, the center of the country's economic and political power, where Jakarta (the capital city of Indonesia) is located. Together with the adjoining smaller islands of Madura and Bali, Java accounts for just over 7% of the land area in Indonesia. These islands are populated by 119 million inhabitants who comprise of 59.5% of the total Indonesian population. The combined populations of the special districts of Jakarta and Yogyakarta and the provinces of West, Central and East Java totaled 120 million people in 1999. The population of the special district of Jakarta was 9.5 million in 1999. By contrast, Papua (formerly Irian Jaya) represents 22% of the total land mass, yet has only 1% of the population. The total population of the island of Sulawesi was over 14.5 million in 1999. Vast areas of Indonesia have very low population levels, while the majority of the people live in the island of Java and Bali.

About 88% of the population is Muslim, 10% is Christian (Protestant and Roman Catholic) and approximately 2% are Hindu and Buddhist. The majority of Indonesians are of Malay ethnicity. The remainders of the “pribumi” (natives) are Melanesian (in Papua-Irian Jaya and the eastern islands). Major ethnic groups of Indonesia are: Javanese (45%), Sundanese (14%), Madurese (7.5%), Coastal Malays (7.5%), and others (26%). For the purpose of classification, according to Fisher (1967) the ethnicity in Indonesia are divided into 2 types: firstly, Deutro Melayu which consists of ethnic Aceh, Minangkabau, Melayu Sumatera, Rejang lebong, Lampung, Jawa, Sunda, Madura, Bali, Makasar, Bugis, Menado, and Minahasa and secondly Proto melayu which consists of Batak, Nusa Tenggara Timur (NTT), Ambon and Papua. There are also Chinese,

Indians and Arabs descendant concentrated mostly in urban areas throughout the archipelago.

3.5.2 Incidence/prevalence of oral cancer in Indonesia

There is unavailable prevalence or incidence data for oral cancer in Indonesia. Reliable data regarding the number of Indonesians who die from cancer are also currently not available. The WHO estimates that 57,000 Indonesians die each year as a result of tobacco use with tobacco-attributable mortality being around 3-4% in 1986 and is increasing dramatically (IARC, 1998). The latest studies done using data collected from 13 histopathological centre in Indonesia found that the ASR rate for oral cancer was 3.16 (both sexes) per 100.000 population. The study obtained data from histopathology laboratory of the Medical Faculty of University of Airlangga, East Java over a period of 1987-1992 where they found that oral malignancies were 45.3% out of 2193 lesions. The incidence of malignant tumours per 100.000 population over the-6 year study period was 2.64 except in 1990 which dropped to 2.1 (Budhy et al., 2001).

3.5.3 Risk habits practiced

3.5.3.1 Tobacco smoking

Indonesia is the fourth largest consumer of tobacco in the world and the second largest market for cigarettes in the Asia Pacific (including kretek). Indonesia has a long historical tradition of tobacco growing and trading. Tobacco is a major part of Indonesia's contemporary economic and cultural life. Tobacco is the Indonesian government's largest sources of revenue after oil, gas and timber which is around US$4 billion in 1999, and it forms about 10% of the Indonesian government's total tax

revenue and this is the second largest contributor of national income (Reynolds, 1999). In the 1990s Indonesia experienced the world's highest increase in cigarette consumption of around 47%. Additionally, it was estimated that 68.8% of men and 2.6% of women smoked in 1995 (World Bank, 1999).

Indonesia is famous for its aromatic *kretek* cigarettes, which are made from mixtures of tobaccos and *cengkih* (cloves). Although several international brands are manufactured locally under license, *kretek* brands produced by Indonesian companies dominate the retail market (Barraclough, 1999). Most cigarettes companies are located in Java island. Approximately 3.4 million workers are involved in all aspects of tobacco industry from growing to retailing (Departemen Pertanian, 1995). Hand rolled kreteks was commercially produced in Indonesia as home industry in 1906 (Hunuz, 2000). This was followed by the production of white cigarettes (tobacco only, without cloves) in 1924 (Reid, 1985). Smoking *kreteks* replaced chewing betel quid during the early to mid 1900s for many rural males, and gained popularity after mechanization of the industry in the 1970s (Reid, 1985).

As mentioned above, *Kretek* is a cigarette containing tobacco, cloves and clove oil. Thus, it gives a distinctive scent during smoking. The anaesthetizing effect of clove oil accounts for their historic use to alleviate sore throats and asthma but also results in high tar yields and potentially extensive lung damage (Hunuz, 2002; Lawrence et al, 2004). *Kreteks* are preferred by 88% of Indonesian smokers (Ministry of Health

of Indonesia, 2004). *Kretek* comprises of 30-40% cloves and spices. Nicotine yields for kretek sold in Indonesia are between 1.7 - 2.5 mg per stick and between 28.1 – 53.2 mg per stick of tar compared with < 0.05 - 1.4 mg nicotine per stick and <0.5 -24 mg tar per stick for cigarettes sold in US (Rahman, 2004; Achadi et al., 2005).

Based on the National Socio-Economic Survey and National Household Health Survey in 1995, the prevalence of smoking in Indonesia in 1995 was 61.3% for men and 2.6% for women aged 20 years and older (Suhardi, 1995) with slight increase in smoking prevalence to 62.2% in 2001 (Ministry of Health of Indonesia, 2004). There are more men than women smokers, and the highest percentage of cigarette smokers is among those aged 40-44 years (74.4%). The prevalence of smokers is higher among those with low education. Almost 50% of the population smokes 11-20 sticks per day, and most smokers have duration of over 30 years (22%). Among urban smokers, the most popular type of cigarette is the filter *kretek* which is smoked by 59.8% of males and 54.3% of female. The second most popular type of cigarettes is non filtered *kretek,* consumed by 20.8% of males and 22.1 % of females. In rural areas, 53.1% males and 60.5% females prefer non-filtered varieties of cigarettes (Suhardi, 1995).

Regionally, the highest male smoking rate is in Gorontalo province (69%) in the northernmost tail of Sulawesi Island compared with the lowest rate in Bali (45.7%). Smoking prevalence during the period 1995-2001 in East Java and Lampung province increased by 60%. The

relatively low educational levels could be a contributing factor to the increase in smoking prevalence. Female smoking prevalence in Papua, East Kalimantan, Central Java and Bali provinces also showed an increase in 2001, although nationwide rates remain below 2%. The vast majority of smokers (68.8%) started their habit before 19 years of age (Ministry of Health, 2004). Overall, it is estimated that tobacco related mortality accounts for 10% of total death in Indonesia or 200,000 annually. The WHO estimates that the majority of deaths in Indonesia (61%) are attributable to non-communicable diseases. Three conditions accounted for three-fourths of non-communicable disease deaths: cardiovascular diseases, malignant neoplasm, and chronic obstructive pulmonary diseases (WHO, 2000b; Nawi et al., 2006).

3.5.3.2 Betel quid chewing

In Indonesia, tobacco is used as part of the betel quid mixture chewed with betel leaf. "*Sirih*" is a term used by Indonesian to mean betel quid. Betel quid chewing is practiced for the most part in rural areas, and betel quid chewing in Indonesia involves the creation of a quid with betel leaf and other ingredients. Historically, the chewing habit was mostly practiced by old women, as a way of showing appreciation to their guests when they visit each other or during a cultural event or wedding.

The betel quid chewing habit practiced by the older generation in most rural areas in Indonesia is decreasing dramatically and has been substituted by tobacco smoking habit of the younger generation in the

face of “modernization”. The 1986 household health survey of seven provinces found that, Java and north Sumatera Islands are the most common places where betel quid chewing is practiced. Besides that, the survey also found that betel quid chewing was predominantly a female practice. Whereas only 3.7% of males surveyed reported that they chewed *sirih*, the rate for females was 16.7%. Among women, the habit was most common in the higher age groups. Although 50.3% of women aged over 60 years chewed *sirih*, only 4.5% of those aged 25 to 29 years did so (Santoso et al., 1987). The latest study on the characteristic of betel quid chewers in *Karo* land, North Sumatera found that the mean age of betel quid chewer was 46.3 years with the average duration of chewing of 12.4 years, frequency of chewing of 11 times per day and the most used type of quid is without tobacco (Hasibuan, 2005). The type of quid used in Karo land was similar to another study done by Permana et al. (1995) in Purwakarta (West Java). In contrast, the most preferred betel quid in central Java is the betel quid which was added with fine cut of tobacco to the betel leaves and containing smears of slaked lime (*kapur)*, slices of ripe areca nut (pinang) and a small amount of a catechin-containing substance called *gambir* (*catechu* or *kath* in India). Betel quid is chewed first and then a large wad of finely cut tobacco is usually used to clean the teeth. In some areas it is kept in the mouth for some time.

3.5.3.3 Alcohol drinking

Alcohol drinking habit is practiced by a small number of Indonesians compared with smoking habit. Similar to cigarette smoking habit,

drinking of alcoholic beverages was first introduced by the Dutch. However the habit is not as popular as smoking and it may be because the majority of Indonesians are Moslem. It is thought that the drinking habit is more deviant than smoking or betel quid chewing. However, alcohol drinking (including the traditional type called “tuak”) is famous in certain ethnic groups in Indonesia, such as the *batak* ethnic group in North Sumatera. This habit is also famous in other places in Indonesia such as the Eastern part of Indonesia.