CHAPTER 1

INTRODUCTION

Malignant neoplasm represents major causes of morbidity and mortality all over the world. Cancer is one of the main causes of death after infections and heart diseases in all societies (Johnson, 2003a) and is the fatal leading disease in the world (Pastides, 2001a). The trend of cancer incidence and mortality are increasing annually. The International Agency for Research on Cancer (IARC) conducted a comprehensive survey on cancer in 10 countries and geographical regions in 1994. The findings indicated that of the 7.6 million new cancer cases that were diagnosed worldwide annually, more than half are estimated to be in developing nations. Lung cancer is the most common cancer among 11 other sites studied, followed by stomach cancer and oral cancer. The latter is especially prevalent in Asia (Pastides, 2001). Furthermore, in terms of number of new cancer cases, Parkin et al. (2005) estimated that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer (within 5 years of diagnosis) in the year 2002.

Oral cavity cancer is the 11th most common type of cancer in the world in term of number of cases (Stewart and Kleihues, 2003b), with age standardize rates (ASR) of 6.3 and 3.2 per 100,000 for males and females respectively (Parkin et al., 2005). Globally, some 389,650 cases of oropharyngeal cancer occurred in the year 2000; 266,672 for the oral cavity and 122,978 for oropharynx (Parkin et al., 2005). Black et al. (1997) reported that oral and pharyngeal sites remained the sixth most common neoplasm within the European Union. In addition mouth and pharynx is the third most common site for malignant disease among men and the fourth among women in developing countries (Johnson, 2003a).

However the geographic pattern and trends in incidence of oral cancer vary widely between countries and geographical areas of the world (Scully and Bedi, 2000). The regional area with the highest ASR is Melanesia (31.5 per 100.000 in men and 20.2 per 100.000 in women respectively). Besides that, ASR for males is also high in Southern Asia (12.7), followed by Western Europe (11.3), Australia/New Zealand (10.2), and the least in Southern Europe (9.2). Similar to the ASR for males, the incidence of oral cancer for females is also relatively high in Southern Asia especially in the Indian subcontinent (8.3) (Parkin et al., 2005). As such, 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. India, Bangladesh, Pakistan and Sri Lanka, are the countries where oral cancer is the most common and accounts for about one-third of all cancer types (Stewart and Kleihues, 2003b).

The difference in distribution of oral cancer worldwide is influenced by their risk factors (Stewart and Kleihues, 2003a). The etiology of oral cancer is multifactorial, whereby tobacco use together with excessive consumption of alcohol has been suggested to account for 75% of the risk for oral and pharyngeal cancer globally especially in Europe, America and Japan (Polednak, 2004). Besides that, tobacco quid or betel quid chewing is also a major causes of oral and oropharyngeal squamous cell carcinoma in the Indian subcontinent, parts of South-East Asia, China, Taiwan and emigrant communities in USA.

In South East Asia, oral cancer often involves the tongue, floor of the mouth, and buccal area which is attributable to chewing betel quid habit. IARC in 2003 reported that cancers of anterior two-thirds of the tongue generally also predominate in developing countries due to smoking and alcohol consumption besides pharyngeal cancers which

are common in developed countries and in Central Europe (Stewart and Kleihues, 2003a). Incidence of tongue cancer consistently is found to be higher (by approximately 50%) in blacks compared to whites within the same regions of the United States. In China, nasopharyngeal cancer is the most common cancer. Its high incidence there has been attributed to viruses, nutritional factors, and occupational exposures (Pastides, 2001).

Several studies have also found that oral cancer risk is associated with dietary intakes, chemical carcinogens, viral exposure, genetic susceptibility and environment (Franceschi et al, 1992). As stated by Doll and Peto (1981), 10-70% of all cancer mortality in the United States could be attributable to dietary factors. Moreover, it has been proven that high consumption of foods rich in substances such as fiber, carotenoids, some vitamins and minerals will reduce risk of certain cancers (Pastides, 2001b; Singh and Gaby, 1991).

Some studies have also reported that specific genetic polymorphisms in metabolism genes have a role in the development of cancer in the oral cavity. An individual's genetic susceptibility to oral cancer may depend on the metabolic balance between phase I enzymes, such as cytochromes P450 (CYPs), and phase II enzymes, such as glutathione S-transferases (GSTs). Multistep carcinogenesis of cancer can develop as a result of several agents or events during the initiation or promotion of malignant transformation. The environmental factors of either biological or chemical origin mentioned above may act as initiators, promoters or both (Schwartz, 2000).

Indonesia is the fourth most populous nation (220 million people) in the world after China, India and the United States. More than half of the population resides in Java,

which is the center of the country's economic and political power. Geographically, Java Island accounts for just over 7% of Indonesia land size, but is populated by inhabitants which comprise of 59.5% of the total Indonesian population. Jakarta, the capital city of Indonesia which is situated in Java Island has a population of more than 10 million. In term of ethnicity, the population of Jakarta is quite representative of the many inhabitants from other islands who migrate to Jakarta.

Despite the high incidence of oral cancer within the Southeast Asian region, a national incidence data for oral cancer in Indonesia is unavailable. So far, frequency of oral cancer in Indonesia, have mainly utilized data from histopathological reports from 13 centers in Indonesia. The study was undertaken by the Ministry of Health, Indonesia in the year 1999 (Departemen Kesehatan Indonesia, 1999). The study reported that the ASR of oral cancer was 3.05 per 100,000. The incidence for male was 3.61 per 100,000 which was higher than for female (2.17 per 100,000). In addition, the study also reported that oral cancer is ranked ninth out of all cancers in Indonesia. Another study had also utilized hospital-based data from pathology department of Medical Faculty University of Airlangga in Java Island for the period 1987-1992. (Budhy et al., 2001). The study which consisted of 2193 tumor cases found that malignancies accounted for 45.3% of cases and of these, 57% was oral cancer. Another study done in Medan, Sumatera Utara which also used histopathological reports from 1995 until 2000, showed that out of a total of 1015 oral lesions, 346 were malignant lesions and among these 34 % was oral cancer (Ginting and Elbritha, 2003)

Oral cancer in Indonesia is usually found in the late stages. This may be due to the failure of early detection of lesions as well as the lack of awareness about the specific risk factors for oral cancer in this population. In spite of oral cancer being the 11th most

common cancer in the world with increasing new cases each year, the Ministry of Health in Indonesia does not give prominence to oral cancer as a priority area in their health programme until 2010. Owing to such lack of prominence given to oral cancer, to date, there is no national survey done on oral cancer prevalence in Indonesia as well as the risk factors associated with it.

Indonesia ranks fifth among the world's leading tobacco consuming countries. It consumes 200 billion of cigarettes annually as 62% of the populations are smokers (Survey Kesehatan Rumah Tangga, 1999). Most tobacco consumed in Indonesia is in the form of cigarettes. Between 85-90% of all cigarettes smoked in Indonesia are *kreteks* which contain higher levels of tobacco-specific nitrosamines which are highly carcinogenic. Hence the Indonesians are most probably at high risk to develop oral cancer and potentially malignant lesions. In addition to smoking, the role of other risk factors such as alcohol consumption, betel quid chewing, dietary intake and genetic susceptibility have also not been fully investigated in the Indonesian population. The dietary pattern varies among the ethnic groups. Although the inter-ethnic variation in the prevalence of oral cancer may be attributed to environmental and lifestyle factors, it is also possible that it may also be due to the differences in their genetic profiles. Asian genetic profiles may differ from those in the Western world. Hence, it is necessary to explore the genetic polymorphism in the Indonesian population in order to verify the applicability of the findings of the developed countries and other developing countries to the Indonesian population

In view of the lack of investigations on associated risk habits and oral cancer, a study on these aspects is very much required. With this study, it may be possible to intervene and advise those with risk habits to modify, or to stop these habits if such study of the

Indonesian population was able to show association with these habits. Primary prevention and an early detection approach would be able to offer a cost-effective option towards a reduction in the overall morbidity and mortality due to oral cancers in Indonesia. The findings of such a study would also provide a data base for future assessment of treatment and the quality of life of oral cancer patients. Additionally, such a study on dietary habits, genetic susceptibility and environment as risk factors in oral carcinogenesis will be very useful in indicating possible chemoprevention strategies. The development of epidemiologic biomarkers may also enhance an understanding of the complex relationship of risk factors including genetic polymorphism and cancer development which will be useful as a basis for early diagnosis and chemoprevention.