CHAPTER 1

INTRODUCTTION

Lung cancer is the most frequent cancer in the world today, and the epidemic of this disease is still ongoing. Globally, carcinoma of the lung is the most common cause of cancer death, and cigarette smoking is widely accepted as the major risk factor for the incidence of lung cancer (Peto et al., 1996). In Thailand, according to a 2004 smoking surveys by the National Statistical Office, Ministry of information and communication technology reported that among adults age 15 and over, the percentage of regular smokers in Thailand was 19.5% which slightly more than one-third (37.2%) of men and 2.1 % of women were smokers. The average number of cigarettes smoked per day was 10.4. The percentage of regular smokers who live in the north is 20.6%, where it has been traditional for women to smoke. Most of the regular smokers are at the age between 15 to 39 years old (91.2%) and the average age of starting regular smoking is 18.4 years old. Furthermore, about 3/5 of those smokers started cigarette smoking before the age of 19 years, a quarter began to smoke between the age of 20 to 24 years and only 6.8% began to smoke after 24 years of age. The mortality rates (per 100,000 populations) from trachea, bronchus and lung cancer are 21.5 in male and 7.4 in female smokers (WHO 2003). In Thailand approximately one third of male cancer deaths and one tenth of female cancer deaths are due to lung cancer. These data indicated that there has been a high smoking rate in Thailand and tobacco smoke-related cancers is the major health problem that should be solved immediately.

It is now accepted that a large proportion of human cancers are caused by synthetic or natural chemical compounds in the environment. Carcinogenic risks from exposure to exogenous chemical carcinogens depend not only on the intrinsic nature and dose of each chemical, but also on individual vulnerability to the carcinogens (Lazarus et al., 1998). Most chemical carcinogens require metabolic activation by Phase I enzymes (cytochromes P450) and detoxification by conjugation via the various Phase II enzymes (epoxide hydrolase, glutathione-S-transferase, N-acetyltransferase, sulfotransferase, etc.) (Ernster et al., 1991). Thus the coordinated expression and regulation of Phase I and Phase II enzymes and their metabolic balance may be an important host factor in determining whether exposure to carcinogens results in cancer or not (Idle, 199; Nebert, 1991).

The cytochromes P450 (CYPs) are a large group of constitutive and inducible haem-containing oxidative enzymes, which have a central role in the oxidative metabolism of a diverse range of xenobiotics. The discovery of the CYPs led to the understanding of inter-individual differences in the metabolism of certain drugs and/or environmental chemicals. The recent studies of carcinogenesis have been focus on inter-individual variation in CYP expression. A number of human CYP genes are now known to polymorphic and the effect of these polymorphisms is often to influence the level of expression and/or functional activity of those CYPs.

For a number of CYP enzymes, mutations have been identified by DNA-based methods which can be correlated with a particular metabolic phenotype. The human CYPs metabolize many compounds, which are mutagenic and/or carcinogenic, altered substrate pharmacokinetics arising from specific mutations can therefore lead to altered toxicity or mutagenicity in affected individuals. As a consequence, mutations

within the human CYPs enzymes have been associated with disease susceptibility. Individuals expressing mutant forms of these proteins may increase ability to activate substrate to its toxic form. Therefore, it is important to determine mutation frequencies within the exposed population and correlate the results obtained with appropriate controls.

CYP2A13 is one of these enzymes believed to play an important role in metabolic activation of xenobiotic toxicity and tobacco-specific *N*-nitrosamines in the respiratory tract such as NNK. The *CYP2A13* gene is polymorphic, to date 20 alleles have been reported on the Human Cytochrome P450 Allele Nomenclature Committee homepage (www.imm.ki.se/CYPalleles/cyp2a13.htm). Some of these polymorphisms may have important clinical and physiological implications individuals homozygous for these variants. This study focused on the frequency distribution of the functional SNPs in the *CYP2A13* gene in Thai population who live in the upper Northern area of Thailand.