CHAPTER I

INTRODUCTION

Lung cancer is a disease of uncontrolled cell growth in tissues of the lung. This dysregulated growth may lead to metastasis, which is invasion of adjacent tissue and infiltration beyond the lungs. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. There are two main types of lung carcinoma, categorized by the size and appearance of the malignant cells that observed by a histopathologist under a microscope: non-small cell lung carcinoma (NSCLC) (80.4%) and small cell lung carcinoma (SCLC) (16.8%). This classification, based on histological criteria, has important implications for clinical management and prognosis of the disease.

1. Incidences of lung cancer

Lung cancer has been the most common cancer in the world. The 1990 global lung cancer incidence rate of 37.5 per 100,000 population gave rise to 771.8 thousand cases. Between 1985 and 1990, lung cancer burden of the developing countries went up by 25% (from 261,000 to 327,100), while that of the develop countries went up by only 7% (1). By the year 2002, there were 1.35 million new lung cancer cases, representing 12.4% of all new cancers. It was also the most common cause of death from cancer, with 1.18 million deaths, of 17.6% of the world total (2).

In Thailand, the first population-based cancer registry was begun in Chiang Mai in 1986. At present, there are five registries actively working in different parts of the country. Provinces representative for the four regions of the country are Chiang Mai and Lampang in the North, Khon Kaen in the Northeast, Bangkok in the Central, and Songkhla in the South. The cancer registry shows that lung cancer is the most frequent malignancy for both sexes in northern region. The annual Age-Standardized incidence Rate (ASR) of lung cancer in males and females in Chiang Mai and Lampang are 36.5, 53.5 or 25.1, 25.3 per 100,000 population, respectively (3). Tobacco smoking is believed to be the main causative factor for the incidence of lung cancer in this area (4). However, other factors are also believed to play the role for example, chronic benign respiratory diseases due to the fungus *Microsporum canis* (5, 6), exposure to indoor radon radiation and mutagenic environmental air (7). However the fact that there are lower incidence rate of oral-pharyngeal cancer, which is also a cigarette-related cancer, than that in Songkhla (3) indicating a need for further studies.

2. Tumor markers of cancer

Tumor markers are substances that can be found in the body when cancer is present. They are most often found in the blood or urine, but they can also be found in tumors and other tissue. They can be products of the cancer cells themselves, or made by the body in response to cancer or other conditions. Most of them are proteins. Actually, cancer is a disease of dysregulation of cell-growth which can be easily cured if it is identified at a very early stage. However, the reason why cancer is still the major cause of death is due to the lack of an ideal tumor marker highly sensitive and specific for cancer.

Nowadays, there are no tumor markers that have characteristics to be an ideal tumor marker, because the lack of high specificity and sensitivity to identify cancer. The majority of tumor markers is not used for screening of cancer but is predictive of recurrence and response to treatment. Screening refers to looking for cancer in people who have no symptoms of the disease, when it is less likely to have spread and is easier to treat. Although tumor markers were first developed to test for cancer in people without symptoms, very few markers have been shown to be helpful in this way. The only tumor marker widely used in screening today is the prostate-specific antigen (PSA) test. PSA is the most commonly tested tumor marker for the prostate gland. It is normally present in low levels in the blood of all adult men. The normal range is 0-4 ng/ml (8). PSA is prostate-specific, not cancer-specific. A variety of conditions can raise PSA levels: prostatitis (prostate inflammation), benign prostatic hypertrophy (prostate enlargement) and prostate cancer (9-12). PSA levels can also be influenced by a number of other factors. Some prostate glands normally produce more PSA than others. PSA levels tend to increase with age and PSA levels can vary with race: African American often have higher PSA levels, while Asian men often have lower PSA levels. PSA seems to have the capability of achieving at least one of the characteristics of ideal tumor marker-tissue specificity; it is found in normal prostatic epithelium and secretions but not in other tissues. It is highly sensitive for the presence of prostate cancer (11). The elevation correlated with stage and tumor volume (13). It is predictive of recurrence and response to treatment. Finally, the antigen has prognostic value in patients with very high values prior to surgery are likely to relapse (14, 15). Unfortunately, PSA is detectable in normal men and often

is elevated in benign prostatic hypertrophy (11), which may limit its value as a screening tool for prostate cancer.

3. Humoral immunity directed against Tumor-Associated Antigens (TAAs) as potential ideal tumor marker for the early detection of cancer

The presence of tumor is thought to induce the release of many proteins into the circulation. There is clear evidence that the immune system, in addition to defending us against pathogens, is also on guard against other threats, including tumor. During our life time, we may experience several undetectable precancerous lesions that can be eliminated from the body through our immune system. Uncontrolled malignant growth will therefore be characterized by the presence of auto-antibodies the precede clinical findings by months or years. The generation of circulating antibodies that bind to self-protein can be regarded as the systemic amplification by the immune system of a signal that indicates the presence of the tumor (16). Several hypotheses have been proposed to explain the increased incidence of autoantibodies in malignancies, which includes host-immune reaction to TAAs, antigenic stimulation as a result of the destruction of malignant cells, or immune dysregulation induced by the neoplastic process. There are at least 3 main categories of TAAs being proposed: (1) those encoded by genes with tumor-specific expression (2) those resulting from point mutation (such as p53) and (3) those encoded by genes that are overexpressed in certain tumor (17).

A number of previous studies have demonstrated that livin and survivin, a group of anti-apoptotic genes, were abundantly over expressed in various types of tumor tissues (18-30), but not in normal adjacent tissues. In addition, expression of these two anti-apoptotic proteins were reported to induce autoantibodies response in

cancer patients (29, 31-37). We, therefore, hypothesized that autoantibodies response to livin and survivin may potentially represented a new tumor marker. From this hypothesis, we plan to generate expression DNA constructs harboring livin and survivin encoding DNA using pET-15b vector in order to produce livin and survivin proteins to detect specific autoantibodies to livin and survivin in sera of cancer patients by ELISA technique. Since lung cancer is a major problem in Northern region and also an organ being exposed to large amount of blood, we therefore, carry out our study in lung cancer. Protein expresstion level of these two genes will also be examined in tumor tissues in comparison to normal tissues in order to determine the correlation between protein expression level of livin and survivin in tumor tissue and the presence of their specific autoantibodies in sera of lung cancer patients as well as their clinical usefulness.