INTRODUCTION

Lung cancer is the leading cause of death from cancer in both men and women **(Jemal et al., 2008).**

There are two main types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Non-small cell lung cancer accounts for about 80% of lung cancers **(Louise, 2010).**

Non-small cell lung cancers (NSCLC) are themselves further classified into three different types: squamous cell lung carcinoma, adenocarcinoma, and large cell lung carcinoma **(Perkins, 2010).**

In the last several decades adenocarcinoma has become the predominant type of NSCLC. **(Gabrielson, 2006; Henschke et al., 2006)**

Recent advances in the treatment of pulmonary adenocarcinoma have increased the need for accurate typing of non-small cell carcinomas **(Bishop et al., 2010).**

Also there is an important differentiation exits between primary lung cancers which originate in the lung, and metastatic (secondary cancers) which spread to the lung from other sites.This distinction is important because staging, treatment, and prognosis are all based upon the primary site of disease **(Hong and Tsao, 2008).**

Napsin A is an aspartic proteinase involved in the maturation of surfactant protein B. It is detected in the cytoplasm of type 2 pneumocytes and alveolar macrophages **(Bishop et al., 2010).**

Napsin-A, which is expressed in lung tissue, is a relatively new marker for lung adenocarcinoma **(Stoll et al., 2010).**

It is expressed in the cytoplasm and is strongly positive in up to 80% of primary lung adenocarcinomas by immunohistochemistry. Squamous cell carcinomas and small cell carcinomas of the lung have been negative for napsin A ***(*Jagirdar, 2008).**

Napsin A is superior to TTF-1 in that its expression is stronger, more diffuse and more sensitive. The strongest staining is seen in lung adenocarcinoma and appears to be specific for a lung primary. **(Jagirdar, 2008).**

AIM OF THE WORK

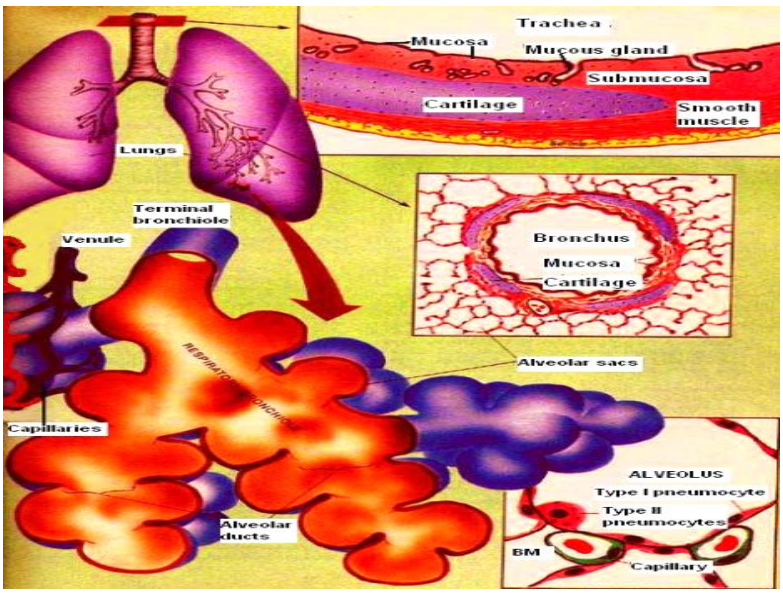
To evaluate retrospectively the utility of napsin A expression in the different types of lung carcinoma and its role in the diagnosis of primary and metastatic lung adenocarcinoma.

REVIEW OF LITERATURE

Histological structure of lung:

The respiratory tract is divided into upper and lower parts. The upper respiratory tract is composed of the nose and larynx, and the lower respiratory tract consists of the tracheobronchial tree and lung. The tracheobronchial tree contains cartilage and submucosal mucus-secreting glands and is lined by a pseudostratified, ciliated columnar epithelium that contains, in addition, goblet cells, clara cells, and kulchitsky cells (neuroendocrine cells). The bronchi ultimately branch into bronchioles that do not have cartilage and submucosal glands. The terminal bronchioles are purely conducting ducts that divide into respiratory bronchioles which merge into alveolar ducts and alveoli **(Nguyen, 2008)**.

Figure (1): Normal anatomy and histology of the lower respiratory system.



(Regamey et al., 2007).

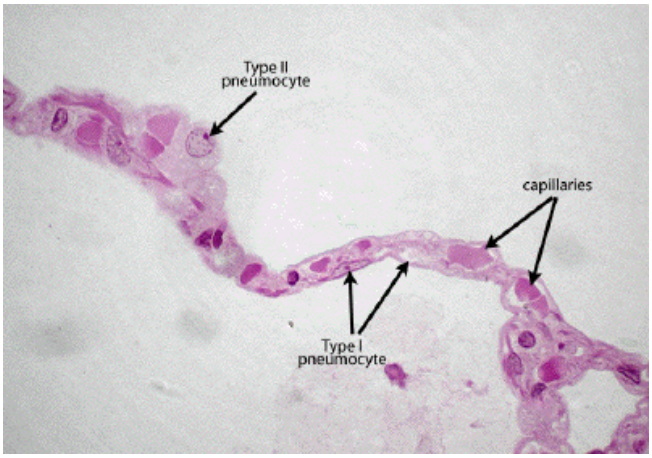
The bronchioles are lined by simple cuboidal epithelium, while the alveoli are lined by simple flattened epithelium and are enveloped by capillaries. Also, to keep the alveoli clean there are macrophages that moved out of connective tissue to the epithelial surface to ingest any foreign material **(Muller et al., 2005).**

The alveolar epithelium contains a continuous layer of two cell types. The first is flattened and cover 95% of the alveolar surface and called type 1 pneumocytes. The other is rounded and called type 2 pneumocytes which secretes the surfactant and involved in the repair of alveolar epithelium after destruction of type 1 cells (**Regamey et al., 2007**).

The lung and the inner aspect of the thoracic cavities are covered by a layer of mesothelial cells **(Nguyen, 2008)**.

The main cell types of the bronchial-bronchiolar epithelium are basal cells, neuroendocrine (kulchitsky-type) cells, ciliated cells, serous cells, clara cells, and goblet cells. Kulchitsky-type cells are part of the diffuse endocrine system. They are numerous in the bronchial and bronchiolar epithelium of the fetus and neonate, but very scanty and difficult to demonstrate in the adult. Small clusters of neuroendocrine cells located within the epithelium of bronchi and bronchioles (and sometimes also at the level of alveoli) are referred to as neuroepithilial bodies; their function is unknown (**Wright *et al.*, 2006).**

Figure (2): the histology of alveolar wall.



(Souba, 2012).

Epidemiology of lung cancer:

Incidence:

Lung cancer has been estimated as the most common cancer in the world for several decades. An estimated 1.61 million people across the world were diagnosed with lung cancer in 2008, accounting for 13% of the total. More than half (55%) of the cases occurred in the developing world **(Wild, 2010).**

Approximately 373,489 Americans are living with lung cancer **(US national institute of health, 2011).**

In 2012, an estimated 226,160 new cases of lung cancer were ascribed to lung cancer in the United States (US), representing almost 14% of cancer diagnoses **(Chen et al., 2012).**

In Australia there are approximately 9700 cases of lung cancer diagnosed each year (small cell and non small cell types) representing about 9% of all cancers (**Olver et al., 2011).**

In Japan, the lung cancer incidence among men and women have increased, particularly in adenocarcinoma (ADC). The age-adjusted incidence rates of ADC among men and women have continuously increased, while those of squamous cell carcinoma (SCC) and small cell carcinoma (SMCC) turned to decrease since 1990s **(Toyoda et al.,2008).**

In Saudi Arabia, more than 250 people are diagnosed with lung cancer each year, according to statistics released by the Saudi National Cancer Registry. The statistics also showed that men are more prone to lung cancer than women and that there had been an upsurge in lung cancer

among women due to an increased use of hookah. This increase coincided with a trend across the Kingdom for coffee shops that employ women exclusively for serving **(fakkar, 2007).**

In Jordan, lung cancer came the third with 356 cases, constituting 7.7 % of the total cancer incidence in 2008 **(Malkawi, 2010).**

Fayek et al. (2007) stated that in Bahrain, There were 541 (7.4%) patients with primary lung cancer. Primary lung cancer ranked the 2nd and the 11th most common cancer in the males and females respectively. It also accounted for 10.8% and 3.4% of all malignancies in the males and females respectively, according to revision of all the histopathology and hematopathology archives from all government and private hospitals and clinics in Bahrain between 1952 and 2004**.**

Lung cancer was the most frequently diagnosed cancer among males in Qatar, accounting for 12.1% of all cases. In females, lung cancer ranked 9th, accounting for 2.8% of all cancer cases in females diagnosed in 2002 statistics **(Ibrahim et al., 2010).**

In Egypt , the incidence of lung cancer has increased significantly over the last few decades in the 1960s and 1970s **(Omar, 2005).**

Mokhtar et al. (2007) reported that primary malignant tumors of the respiratory system were the fifth most common tumor received at the surgical pathology department in the National Cancer Institute (NCI) during the years 2003-2004 constituting 5.9% of total malignancy , with high male predominance of 73%. Malignant lung

tumors were 24.16% of tumors of the respiratory system and 1.54% of total malignant tumors**.**

In 2006 lung cancer cases were 47000 case, representing 0.06% of the total Egyptian population **(Govindan *et al.*, 2008).**

Khaled (2006) stated that accurate data on the incidence of cancer in Egypt are not available, however, estimates from the Gharbiah population-based cancer registry and the National Cancer Institute hospital-based registry suggest about 100 000 cases a year are being diagnosed. Due to the age structure of the population, the mean age is lower than in Western countries and lower among females than males.

Khaled (2006) also stated that as the lung cancer epidemic is at an earlier stage among women, lung cancer is not yet one of the top ten diseases causing mortality among females. Most diagnosed cases are advanced and the commonest type is adenocarcinoma followed by common squamous-cell carcinoma. Lung cancer is the fifth most common cancer among males presenting at the National cancer Institute in Egypt after bladder cancer, lymphoma, liver cancer and leukaemia.

According to Ain Shams University Hospital and Ain-Shams Specialized Hospital, The relative frequency of lung cancer cases received was 0.96% from the total malignancies. The non small cell lung cancer cases (NSCLC) represented 93.5% of lung cancer and the small cell lung cancer (SCLC) represented 6.5% of lung cancer cases **(Khalil et al, 2009).**

Age and sex:

In men, lung cancer is the second most common cancer after prostate cancer, responsible for 15% of all new male cancer cases. For women, it is the second most common cancer after breast cancer, accounting for 12% of all new female cases **(Cancer Research UK., 2010).**

Wild (2010) reported that lung cancer incidence is more than double in men than in women worldwide (rate ratio 2.5 : 1.0).

Chen et al. (2012) stated that the incidence rate of lung cancer is declining significantly in men, from a high of 102.1 cases per 100,000 in 1984 to 71.8 cases in 2007. In women, the rate has begun to decrease after a long period of increase.

Eldridge (2010) mentioned that lung cancer is the leading cause of cancer death for women in the United States, accounting for almost twice as many deaths as breast cancer. The incidence of lung cancer is greater in men than in women, but women are catching up. Unlike men, a greater percentage of women that develop lung cancer have never smoked and roughly 20% of lung cancer deaths in women occur in lifelong nonsmokers.

Eldridge (2010) mentioned that women are more likely to survive lung cancer at all stages of the disease. This survival advantage over men is greatest for local disease,where surgical treatment of lung cancer offers a greater chance for a cure in women than in men. Women tend to be slightly younger, by an average of two years, at the age of diagnosis than men.

Lung cancer is rarely diagnosed in people younger than 40, but incidence rises steeply thereafter peaking in people

aged 80-84 years. Most cases (87%) occur in people over the age of 60 **(Ferguson and Wilkinson, 2010).**

In the 1950s the male/female ratio for lung cancer cases was 6:1 but with decreasing male rates and increasing female rates, the ratio is now 1.3:1 **(cancer research UK, 2010).**

In the US from 2004-2008, the median age at diagnosis for cancer of the lung and bronchus was 71 years of age. Approximately no one (0.0%) were diagnosed under age 20; (0.2%) between 20 and 34; (1.6%) between 35 and 44; (8.8%) between 45 and 54; (20.9%) between 55 and 64; (31.1%) between 65 and 74; (29.0%) between 75 and 84; and (8.3%) 85+ years of age. The age-adjusted death rate in 2004-2008 was 51.6 per 100,000 men and women per year **(Howlader et al., 2010).**

Race :

Villar (2011) reported that among men, black men were diagnosed with lung cancer most often, followed by white, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic men. Overall, 80.5 out of every 100,000 men were diagnosed as lung cancer in 2007. Among women, white women had the most new cases of lung cancer, followed by black, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic women. Overall, 54.5 out of every 100,000 women were diagnosed as lung cancer in 2007.

Underwood et al. (2011) reported that during 2004 to 2006 lung cancer incidence rates in US were highest among men, Blacks, persons aged 70 to 79 years, and those living in the South. Among Whites, the highest lung cancer incidence rate was in the South; the highest rates among

Blacks and American Indians/Alaska Natives in the Midwest, Asians/Pacific Islanders in the West, and Hispanics in the Northeast.

Geographical distribution:

The geographic distribution of lung cancer shows marked regional variation:age-standarised incidence rate range more than 60 fold among men and 30 fold among women. Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America, In contrast, African-American individuals in the United States, an epicenter, now experience lung cancer incidence rates that are among the highest in the world **(Alberg et al., 2007)**.

Age-specific lung cancer incidence rates were between1.5 to 2.3 times higher for more developed countries compared with less developed countries within each age group **(Youlden et al., 2008).**

Morbidity /Mortality:

Wild (2010) stated that lung cancer is the most common cause of death due to cancer worldwide. It is estimated to be responsible for nearly one fifth (18%) of cancer deaths in 2008. Survival from lung cancer is poor in both developing and developed regions of the world.

Chen et al. (2012) stated that lung cancer accounts for more deaths than any other cancer in both men and women. About 27% of all cancer deaths, was ascribed to lung cancer in 2011. Since 1987, more women have died each year from lung cancer than from breast cancer. The decrease in death rates began in men in 1991, and this decrease was augmented to reach 3.0% per year in 2005.

Female lung cancer death rates have been decreasing by 0.9% per year since 2003 after continuously increasing since at least 1930.

Lung cancer is responsible for nearly a quarter (24%) of all male cancer deaths and more than a fifth (21%) of all female cancer deaths. More than three-quarters of lung cancer patients die at age 65 and over, but due to the very large numbers of lung cancer deaths overall, over 4,000 people die from lung cancer before the age of 60 (**Cancer Research UK., 2010**).

In United States, 158,683 people in the United States died from lung cancer, including 88,329 men and 70,354 women in 2007 **(U.S. Cancer Statistics Working Group, 2010).**

Risk factors and Pathogenesis:

There are several risk factors of lung cancer discussed as follow:

1- Tobacco smoking:

Hong and Tsao (2008) stated that cigarette smoking is the most important cause of lung cancer, accounting for about 85% of cases. The risk of cancer differs by age, smoking intensity, and smoking duration; the risk of cancer declines after smoking cessation, but it never returns to baseline. About 15% of people who develop lung cancer have never smoked.

Smoking causes almost 90% of lung cancer deaths. The link between lung cancer and cigarette smoking was first established in 1950 **(Cancer Research UK., 2011).**

Compared with non-smokers, those who smoke between 1-14 cigarettes a day have eight times the risk of dying from lung cancer and those who smoke 25 or more cigarettes a day have 25 times the risk. However, risk is more dependent on duration of smoking than consumption: smoking one pack of cigarettes a day for 40 years is more hazardous than smoking two packs a day for 20 years **(Lubin, 2007).**

Chen et al. (2012) stated that the risk of lung cancer is Just as high in smokers of “light” or “low tar”yield cigarettes as in those who smoke” regular” or “ full flavoured” products.

The exposure to environmental tobacco smoke (ETS) at home or at work among non-smokers increases risk by about a quarter. Heavy exposure doubles risk **(Stayner et al., 2007).**

Inhaling secondhand smoke causes lung cancer in nonsmoking adults. Approximately 3,000 lung cancer deaths occur each year among adult nonsmokers in the United States as a result of exposure to secondhand smoke **(Sebelius, 2010).**

Also the cyclo-oxygenase enzyme COX2 is activated both by oncogenes and the carcinogens in tobacco smoke, and is frequently over-expressed in NSCLC, where it is associated with a worse prognosis in early-stage disease. Overexpression of COX2 is linked to inhibition of apoptosis and increased angiogenesis and metastasis. A clinical trial has demonstrated that the COX2 inhibitor celecoxib can enhance the response to chemotherapy in early-stage NSCLC **(Hirsch and Lippman, 2007).**

A genome-wide association study in never smokers with lung cancer found that a single nucleotide polymorphism (SNP) at chromosome 13q31.3 was associated with an increased risk of non-small cell lung cancer. This observation was validated in several additional cohorts of nonsmokers with lung cancer **(Li et al., 2010).**

2-Hookah smoking:

Hookah smoking is as tough on lungs as cigarettes. The exhaled carbon monoxide in participants was an average of 42 parts per million, higher than that reported in cigarette smokers (17 parts per million) **(Hammond, 2008).**

Smoking a water pipe for 45 minutes produces 36 times more tar than smoking a cigarette for five minutes. Tar -- or "nicotine-free, dry particulate matter" -- contains the cancer-causing constituents of the smoke, although it's not