Introduction

Lung cancer is the leading cause of cancer related mortality in the world. The American Cancer Society estimated that in 2013, the disease will account for almost 159,500 deaths in the United States or approximately 27% of all cancer deaths in the country. Lung cancer accounts for about 14% and 12% of all new cancer diagnoses in males and females, respectively, and nearly 70% of patients with lung cancer will present with locally advanced or metastatic disease at initial diagnosis ***(Robert, 2013)***.

Lung cancer is a highly prevalent malignancy that is associated with substantial morbidity and mortality. Histologically, it is divided into non-small cell lung cancer (NSCLC), the more common form, and small cell carcinoma. Approximately 85% of lung tumors are NSCLC, which comprise three major histological subtypes: adenocarcinoma, squamous cell carcinoma and large-cell carcinoma ***(Ioanna et al., 2013)***.

Initiation and progression of lung carcinoma is the result of the interaction between genetic, epigenetic and environmental factors. Epidemiological studies indicate that cigarette smoking has a strong association, since approximately

80–90% of lung cancers are attributable to cigarette smoking ***(Alberg et al., 2007)***.

According to the National Cancer Institute, lung cancer is the number one cause of cancer-related death in the United States. Because five-year survival rates are generally less than 5% for patients with advanced, metastasized lung cancer, development of effective screenings for early-stage lung cancer is vital ***(Cirino, 2010)***.

Early detection of lung carcinoma could change the disease outcome; the survival rate can increase dramatically. In the effort to improve early detection, many imaging and cytology-based strategies have been employed ***(Schwartz et al., 2007)***.

Recent attention has focused on EBC as a non invasive method for studying the composition of airway lining fluid; it contains aerosol particles in which several non volatile compounds have been identified. EBC analysis of inflammatory biomarkers; (that might reflect the different aspects of lung inflammation or oxidative stress, which is an important component of inflammation) is a non invasive method which has the potential to be useful for monitoring airway inflammation in patients with respiratory diseases ***(Paolo, 2007)***.

Several biomolecules have been detected in EBC of healthy subjects and of patients with different inflammatory lung diseases. Recent evidences have highlighted the relevance of inflammation as a possible trigger of cancer development. Nowadays, an increasing interest is being generated for the studying of lung cancer markers in Exhaled breath condensate (EBC), precisely because this sample seems to lend itself to lung cancer early screening and follow-up ***(Peebles et al., 2007)***.

An interesting inflammatory marker studied recently in lung cancer is ferritin. Ferritin is an iron-storing protein, was initially measured in the serum of patients affected by lung cancer and found to have increased. Elevated levels of ferritin in the serum of patients with non small cell lung cancer (NSCLC) were attributed to an inflammation rather than to body iron overload. Ferritin also measured in samples from airways such as bronchoalveolar lavage (BAL) and bronchial secretion. The source of ferritin in airways is postulated as stemming from the transudation of serum iron into airways ***(Kukulj et al., 2010)***.

Aim of the Work

The aim of this work is to detect lung cancer early by estimating ferritin in exhaled breath condensate with comparison of ferritin level in EBC of COPD patients and to verify its role as a non invasive marker in lung cancer.

Lung Cancer

Lung cancer is the most commonly diagnosed cancer and causes more deaths than any other cancer ***(Ferlay et al., 2002)***. Its high mortality rate results from both a high incidence rate and a low survival rate, with only 14% of US lung cancer patients surviving 5 years after diagnosis ***(Ries et al., 2003)***. Lung cancer is also the leading cause of cancer death in most countries ***(Devesa et al., 2005)***.

Among US men and women, lung cancer is the leading cause of cancer mortality, expected to account for 27% of all cancer deaths in 2013. Whereas lung cancer incidence and mortality rates have been declining over the past two decades in men, rates began to decrease only recently after a long period of increasing rates in women. These trends reflect historical differences in smoking initiation and cessation ***(American Cancer Society, 2013)***.

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). This distinction is essential for staging, treatment, and prognosis. Other cell types comprise about 5 percent of malignancies arising in the lung ***(David et al., 2011)***.

Incidence

International variations in the incidence of lung cancer are striking, with age-standardized incidence rates (ASRs) per 100,000 below 10 in parts of Africa, China, and South America, and over 100 in some Black populations in the United States ***(Parkin et al., 2002)***.

Globally, lung cancer has been the most common cancer diagnosed each year since 1985. Lung cancer had a higher incidence among males worldwide than any other cancer, followed by prostate cancer and stomach cancer. Among females, lung cancer was the fourth most diagnosed cancer, behind breast cancer, cervical cancer and colorectal cancer ***(Parkin et al., 2005)***.

Age-specific lung cancer incidence rates were between 1.5 to 2.3 times higher for more developed countries compared with less developed countries within each age group. There was also a significantly higher proportion of lung cancer patients aged 65 years and over at diagnosis within more developed countries (62% compared with 49% in less developed countries). This primarily reflects the higher life expectancy and different age distribution in more developed countries compared with less developed countries ***(GLOBOCAN, 2002)***.

Risk Factors

A number of environmental and life-style factors have been associated with the subsequent development of lung cancer, of which cigarette smoking is the most important ***(David et al., 2011)***.

Not all lung cancer is smoking related. Other risk factors include exposure to asbestos, haloethers, polycyclic aromatic hydrocarbons, nickel, and arsenic. Interest has also focused on the potential roles of exposure to environmental tobacco smoke (passive exposure to "second-hand" smoke) and to radon. Potential risk factors include dietary factors, genetic factors, and the presence of underlying benign forms of parenchymal lung disease, including chronic obstructive lung disease and pulmonary fibrosis ***(David et al., 2011)***.

1) SMOKING

Smoking prevalence fell among both men and women from 1975 to 2006 ***(Jemal et al., 2008)***. This was accompanied by both a decline in the death rate for lung cancer among men and a leveling off of the death rate for lung cancer among women. The possibility that inhalation of cigarette smoke might be a common cause of lung cancer was first suggested by Adler in 1912 ***(Adler, 1912)***. The evidence linking cigarette smoking to human lung cancer has included a large volume of both

prospective and retrospective epidemiologic research. Well-established criteria, based upon observational evidence, have been described for the attribution of causality to the association between disease and a disease-associated variable. These include:

- Consistency
- Strength
- Specificity
- Temporal relationship
- Coherence

(A Report of the Surgeon General, 1982)

The evidence linking cigarette smoking to lung cancer has been primarily indirect. However, a direct link between tobacco and lung cancer was established, based upon the finding that a specific metabolite of benzopyrene, a chemical constituent of tobacco smoke, damages three specific loci on the p53 tumor-suppressor gene that are known to be abnormal in approximately 60 percent of cases of primary lung cancer ***(Denissenko et al., 1996)***. Related polycyclic aromatic hydrocarbons found in smoke appear capable of targeting other lung cancer mutational hotspots ***(Smith et al., 2000)***.

Estimates of the relative risk of lung cancer in the long-term smoker compared with the lifetime nonsmoker vary from 10- to 30-fold. The cumulative lung cancer risk among heavy smokers may be as high as 30 percent, compared with a lifetime risk of lung cancer of 1 percent or less in nonsmokers ***(Samet, 1991)***. The risk of bronchogenic carcinoma is proportional to the total lifetime consumption of cigarettes. The relative risk increases with both the number of cigarettes smoked per day as well as the lifetime duration of smoking ***(Mattson et al., 1987)***. Additional factors include:

- Age at onset of smoking
- Degree of inhalation
- Tar and nicotine content of the cigarettes
- Use of unfiltered cigarettes.

(Harris et al., 2004)

Second hand smoke

The intensity of exposure to environmental tobacco smoke (passive or "second-hand" exposure) is far less than that which occurs with active smoking. On the other hand, exposure to environmental tobacco smoke usually begins much earlier in life than it does with active smoking, and the duration of exposure to carcinogens occurs over a longer period of time. Epidemiologic studies have now shown that nonsmokers

exposed to high levels of environmental tobacco smoke demonstrate an increased risk of lung cancer compared to individuals with lower cumulative exposures ***(Hackshaw et al., 1997)***.

The risk for the development of lung cancer in response to environmental tobacco smoke may be influenced by genetics. One study found a significant increase in polymorphisms in the gene glutathione S-transferase M1 among 51 nonsmoking women with exposure to environmental tobacco smoke who developed lung cancer compared with 55 nonsmoking women with lung cancer who had no environmental tobacco smoke exposure. Glutathione S-transferase M1 is believed to play a role in detoxifying carcinogens in tobacco smoke; thus, mutations that decrease its activity could serve to promote tumorigenesis ***(Bennett et al., 1997)***.

The amount of cigar smoke to which the lungs of cigar smokers are exposed varies widely (according to carboxyhemoglobin levels). This probably reflects differences in the number of cigars smoked, the depth of inhalation and the degree to which each cigar is smoked to completion ***(Smith and Landaw, 1978)***.

Pipe smoking increases the risk of lung cancer. The increased risk of lung cancer due to pipe smoking is similar to cigar smoking, but less than cigarette smoking ***(Henley et al., 2004)***.

The carcinogenicity of marijuana smoking is less studied than that of tobacco smoking. Several reports have documented histologic and molecular changes in the bronchial epithelium of marijuana smokers that are similar to the metaplastic premalignant alterations that are seen among tobacco smokers ***(Mehra et al., 2006)***.

The carcinogenicity of cocaine smoking is less studied than that of tobacco smoking. There is some evidence that cocaine smokers have histologic and molecular changes in the bronchial epithelium that are similar to the metaplastic premalignant alterations seen among tobacco smokers ***(Barsky et al., 1998)***.

2) OCCUPATIONAL AND ENVIRONMENTAL CARCINOGENS

Numerous occupational and environmental carcinogens increase the risk of lung cancer. The best known factors are asbestos and radon; other exposures include arsenic, bischloromethyl ether, chromium, formaldehyde, ionizing radiation, nickel, polycyclic aromatic hydrocarbons, hard metal dust, and vinyl chloride ***(Marshall et al., 2007)***.

Asbestos

Asbestos exposure is a risk factor for lung cancer to which there can be occupational or non occupational exposure.

The risk of lung cancer associated with asbestos exposure is dose-dependent but varies according to the type of asbestos fiber, the risk appears to be considerably higher for workers exposed to amphibole fibers than for those exposed to chrysotile fibers ***(Hughes and Weill, 1994)***.

The increased risk of lung cancer associated with asbestos is greatly magnified by coexisting exposure to tobacco smoke. The relative risk depends upon the magnitude of the exposure both to cigarette smoke and to asbestos. Workers with asbestosis are at greater risk. The relative risk depends upon the magnitude of the exposure both to cigarette smoke and to asbestos ***(Weiss, 1999)***.

Non occupational asbestos exposure increases the risk of lung cancer. The potential risk is of great public health concern because of the large number of individuals who work or attend school in buildings that contain asbestos, and the cost and potential hazards of asbestos removal. The United States Environmental Protection Agency (EPA) standards for low-level asbestos exposure are based upon linear extrapolation of data from occupational settings to non occupational airborne concentrations that are approximately 100,000-fold less ***(Camus et al., 1998)***.

Radon

Radon is a gaseous decay product of uranium-238 and radium-226, which is capable of damaging respiratory epithelium via the emission of alpha particles. Underground uranium miners who were occupationally exposed to radon and its decay products have an increased risk of lung cancer ***(Grosche et al., 2006)***, and there is an interactive effect between radon exposure and cigarette smoking ***(Field et al., 2000)***.

3) GENETIC FACTORS

Familial risk

A number of studies suggest that first-degree relatives of individuals with lung cancer have an increased risk of developing lung cancer ***(Coté et al., 2005)***. In most studies, this excess risk of lung cancer in close relatives persists after adjustment for age, gender, and smoking habits. A meta-analysis of 28 case-control studies and 17 observational cohort studies revealed an increased lung cancer risk associated with having an affected relative (relative risk 1.8, 95% CI 1.6-2.0) ***(Matakidou et al., 2005)***. The risk was greatest in relatives of patients diagnosed with lung cancer at a young age and in those with multiple affected family members. Other studies have found a lesser, but still significant risk for lung cancer in

second-degree and third-degree relatives ***(Jonsson et al., 2004)***. The increased risk in relatives of patients with early onset lung cancer appears to extend to non-lung malignancies ***(Naff et al, 2007)***.

Specific genes

Advances in molecular biology are beginning to identify specific single nucleotide polymorphisms (SNPs) or mutations that influence the risk of lung cancer. A genome-wide association study in never smokers with lung cancer found that a SNP at chromosome 13q31.3 was associated with an increased risk of non-small cell lung cancer ***(Li et al., 2010)***. This effect appeared to be mediated through a down regulation of the glypican 5 (GPC5) gene. In another study, carriers of the most common mutation associated with cystic fibrosis (delta F508) had a decreased incidence of lung cancer compared with matched controls ***(Li et al., 2010)***.

4) INFLAMMATION

Chronic inflammation is associated with lung cancer. An observational cohort study followed 7081 patients without a known malignancy for approximately 10 years. Among the 6273 patients who had their C-reactive protein level (an indicator of inflammation) measured, the likelihood of developing lung cancer was increased if the C-reactive protein level was greater than 3 mg/dL ***(Siemes et al., 2006)***.

A retrospective cohort study of 10,474 patients with COPD found that the risk of lung cancer was decreased among patients taking inhaled corticosteroids at a dose ≥1200 mcg/day, compared to patients not taking inhaled corticosteroids or taking lower doses ***(Parimon et al., 2007)***.

5) DIETARY FACTORS

Antioxidants

An extensive body of literature suggests that low serum concentrations of certain antioxidant compounds, especially derivatives of vitamins A and E, are associated with the development of lung cancer ***(Woodson et al., 1999)***. Numerous epidemiologic surveys suggested that high levels of beta-carotene in the diet or in the blood were associated with a lower risk of cancer in general and lung cancer in particular ***(Nowak, 1994)***. In addition, an increased consumption of fruit, green and yellow vegetables, and possibly some micronutrients may be associated with a substantially lower risk of lung cancer, both among cigarette smokers and nonsmokers ***(Miller et al., 2004)***.

Flavonoids

The flavonoids are plant metabolites that have antioxidant, antiestrogenic, and antiproliferative properties. Sources include citrus fruits, parsley, onions, berries, tea, dark chocolate.