Introduction

Lung cancer is currently the most common cause of cancer mortality in the world . Although lung cancer has long been the leading cause of cancer death in men , the rate of increase in the men has declined over the past five years . However , over 20% of women expected to die from lung cancer than from breast cancer. Despite the advances in the detection and treatment of lung cancer , over all 5- years survival still remains grim **(Pirozynski ,2006 and Silvestri , 2008) .**

Gorlova et al .(2007) noted that pathogenesis of lung cancer is closely associated with tobacco smoking . Continuous exposure of smoking carcinogens result in accumulation of genetic abnormalities that transform normal bronchial epithelium to neoplastic tissues . Furthermore , epidemiologic studies suggest that lung cancer aggregates in families . There is an increased risk for developing lung cancer for first degree relatives of young age , non smoking lung cancer cases**.**

Giuliani et al .(2007) found that many of genes involved in the development of lung cancer . They have found that turning off the activity of certain cancer – blocking genes called tumor suppressor genes such as P53 and Rb , and turning on various cancer – promoting genes such as C-MYC , ras and bcl-2 may play roles in triggering lung cancer . More recently , scientists have identified gene associated with a cluster of inherited lung cancer . The challenge researchers to turn this knowledge into advances in diagnosis , therapy or prevention .

Many other risk factors are related to occupational agents as arsenic , asbestos and radon that act as lung cancer carcinogens . Moreover , patients with history of chronic bronchitis or emphysema also have a risk factor **(Enstrom &Kabat ,2003 and Panani &Roussos , 2006) .**

The histological classification of lung cancers is based upon the 2004 who classification .Lung cancer is divided in two histological groups , non-small cell lung cancer carcinomas ((NSCLCs) and small cell lung carcinomas (SCLCs) **(Junker, 2006 and Panani&Roussos,2006).**

Non small cell lung cancer is more common than cell lung cancer accounting for 85% of all cases of lung cancer and can be divided into : squamous (epidermoid) cell carcinoma , adenocacinoma , large cell

carcinoma and undifferentiated carcinoma . The proportion of lung cancer have changed . adenocarcinoma has become the most frequent histologic type approximately 40% while squamous , previously the most common , account for approximately 20% to 25% of lung cancer and small cell cancer for 15% **(Pirozynski,2006 and Blackhall &Shepherd , 2007) .**

SCLCs express properties of neuroendocrine (NE) , whereas most of NSLCs lack these properties . Small cell lung cancer (SCLC) is also distinguished from non-small cell lung cancer (NSCLC) by its high growth fraction , and the early development of widespread metastases **(Rosti et al ., 2007) .**

Although considered highly responsive to chemotherapy and radiotherapy , SCLC usually relapses and becomes refractory to treatment within one to two years **(Athony Elias,2007) .**

In lung cancer , disease stage at diagnosis is a major factor in determining how to treat the cancer and how long the patient can be expected to live . Staging is based on the results of physical and surgical examinations, laboratory and imaging tests, and biopsies. To determine the stage , first categorize each tumor by size and by how far it has extended by the TNM system **(Bach ,2008) .**

Small cell lung cancer (SCLC) is primarily treated by means of anti neoplastic chemotherapy , independently of the tumor stage **(Junker, 2006)** . However , in non-small cell lung carcinoma (NSCLC) , stage is the main determinant of prognosis and the basis for deciding options for treatment . Patients with early-stage tumor (1 and 2) are treated by complete surgical resection, which is curative in 40-70% of patients while stage 3 patients required combined modality approached that many include chemotherapy , radiation and surgery **(Alberts ,2007).** Therefore , the distinction between SCLC and NSCLC is still of particular importance (**Dubey and Powel , 2008).**

Aim of the work

A comprehensive review of the histopathology of the different histological types of non small cell lung carcinoma , their subtypes , prognostic factors including staging , cytogenic abnormalities and immunohistochemical staining features .

Review of literature

Embryology and anatomy :

Developmentally , the respiratory system is an out growth from the ventral wall of the fore gut . The mid line trachea develops two lateral out pocketing , the lung buds **(Tobin , 2003).**

Regamey et al .(2007) stated that at birth the lungs are pinkish in color while in adult life the color is dark grey ,mottled in patches and as age advances the color becomes black. As a rule , the posterior border of the lung is darker than the anterior . The right lung usually weights about 625 gm, the left 567 gm and the right lung is shorter by 2.5 cm than the left. However , much variation occurs according to the amount of blood or serous fluid they may contain. Also , the lungs are heavier in males than in females .

Each lung has apex , base, three borders and two surfaces. The left lung divides into two lobes and gives rise to 2 main bronchi while the right lung divides into three lobes with 3 main bronchi. The root of the lung consists of the bronchus , the pulmonary artery and veins , plexuses of nerves , lymphatic vessels , bronchial lymph glands and areolar tissue , all enclosed by reflection of pleura **(Rose and Voynow ,2006).**

Histological structure of lung :

According to **Muller et al .(2005)** the lungs are composed of an external serous coat, a subserous areolar tissue and parenchyma. The bronchioles differ from bronchi by lacking to cartilage and sub mucosal glands. Further branching from the terminal bronchioles the alveolar ducts and finally the alveolar sacs. The bronchi are lined by pseudostratified columnar epithelium which is ciliated and includes goblet cells , and the bronchioles are lined by simple cuboidal epithelium , while the alveoli lined by simple sqamous epithelium and the alveoli enveloped by capillaries. Also, to keep the alveoli clean there is macrophages that moved out of connective tissue to the epithelial surface ingest any foreign material **.**

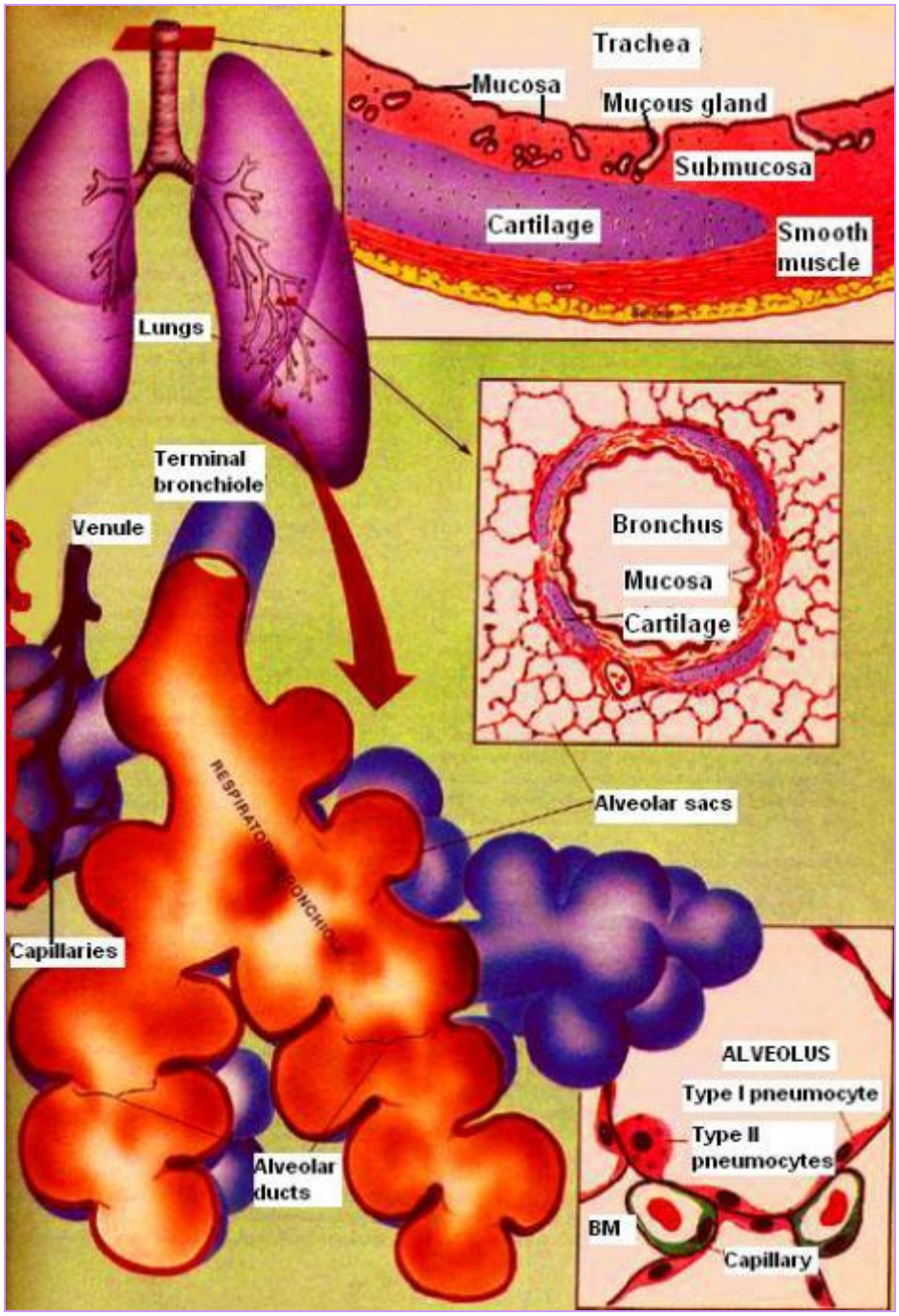
The alveolar epithelium contains a continuous layer of two cell types. The first is flattened and cover 95% of the alveolar surface and called type 1 pneumocytes. The other is rounded and called type 2 pneumocytes which secretes the surfactant and involved in the repair of alveolar epithelium after destruction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

The 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).**

Physiology of the lung :

Contraction and relaxation of the muscles of the chest and the diaphragm are responsible for inspiration and expiration . When air is inhaled , the diaphragm contracts and flattens and the intercostal muscles between the ribs contract , pulling the ribcage upwards and outwards . During exhalation , the intercostal muscles and the diaphragm relax , pulling the ribcage down and contracting the lungs .This reduces the volume of the chest and forces the air out of the lungs . The respiratory centre , located in the brain stem , controls breathing . Although breathing is an involuntary process, the depth and rate of breathing can be altered voluntarily . Oxygen from inhaled air passes through the alveoli into the blood stream . The blood is then taken to the left side of the heart via the pulmonary veins , and from here it is pumped around the body . Deoxygenated blood which returns from the body to the right side of the heart , is pumped back to the lung via the pulmonary arteries . Carbon dioxide passes from the capillaries which surround the alveoli, into the alveolar spaces ,and is breathed out **(Rimer et al ., 2005) .**

Anatomy and Histology of the Normal Lung and Airways



Epidemiology of lung cancer :

Incidence:

According to **Watson et al .(2008)** lung cancer remains the most common malignancy since 1985, and by 2007 there are 1.04 million new cancer cases each year worldwide , which accounts for 12.8% of new cancer cases . About 58% of new lung cancer cases occur in the developing world . It is also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the world total.

Percy and Sobin (2003) mentioned that there were a report initiated by the National Cancer Institute (NCI) about cancer incidence and survival in United States . This report stated that from 1973 through 1986 , lung cancer incidence increased for all race/sex groups except white males. Although overall incidence for males remained substantially higher than that for females during 1973-1986, the trend for males increased at an average of 1%-2% per year, compared with an average increase of 5%-6% for females. During 1982-1986, however, the annual rate of increase for white females was 2%, compared with greater than 8% for black females .

According to **Young(2003)** lung cancer cases in the period 1996-1998 in US , represented the second frequent cancer after cancer prostate in males and after breast cancer in females

Walker and Brin (2005) stated that incidence of lung cancer has decreased significantly by 1.8% per year from 1991 to 2004 among men and remained level from 1998 to 2004 among women. In 2004 there were 173.770 new cases of lung cancer in the US (93.110 new male cases and 80.660 new female cases).

Doll et al .(2008) reported that there were an estimated 215,020 new cases and 161,840 deaths in 2007 in men and women combined of lung cancer in the United States which represented 13% of all other malignancies and adenocarcinoma is the most common type of lung cancer.

In United Kingdom in 2004 there were 37.000 cases of lung cancer (22.000 males and 15.000 females)accounting for 14% of all newly diagnosed cases of malignancies . In men, lung cancer is the second most common cancer after prostate cancer, responsible for 16% of all new male cancer cases. For women, it is the third most common cancer after breast cancer and bowel cancer, accounting for 11% of all

new female cases. The main types of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell carcinoma, which account for approximately 35%, 27% and 10% of all lung cancer cases respectively in the UK. While cigarette smoking has been linked to all four types of lung cancer, adenocarcinoma, is the most common type in non-smokers **(Ferlay et al ., 2007).**

In Japan specifically, the estimated incidence of lung cancer was 85,000 cases in 2005 **(Oshima et al ., 2007).**

Ries et al .(2007) reported that there were 2.950 new cases of lung cancer in New South Wales (NSW) in 2005 (1.784 males and 1.166 females) , represented 11.5% of all other malignancies .

Baron et al .(2002) mentioned that between 1981 and 1995 the national cancer register in Israel received reports on 13,600 new cases of lung cancer. They evaluated the trends in total lung cancer and the histologic subtypes, in Jewish and Arab Israelis. During this period, the age-adjusted incidence of lung cancer increased in the male Arab population, while for male Jews there was a non-significant decrease, for women in both population groups the rates were stable. When analyzed by age group, there was a significant decrease in incidence rates in Jewish males aged 75 years and older. An analysis by histologic subtypes showed two different trends. In the Jewish population, the age adjusted incidence rates of squamous cell carcinoma (SQCC) decreased and the incidence rates of adenocarcinoma (AC) increased, whereas in the Arab population the incidence rates of both subtypes increased, although statistically significantly only for SQCC. The changes found in the Jewish population are similar to those found in other western countries, where the rates of AC are increasing and the rates of SQCC are decreasing. The trends in the Arab population in Israel are different. This may be due to different trends in the prevalence of smoking in the two populations.

Young (2003) mentioned that lung cancer cases in Saudia Arabia in the period between 1996-1998 represented 6% of all male cancer cases reported in this period , the fourth frequent cancer after liver cancer , non-Hodgkin lymphoma and leukemia.

According to **Parkin et al. (2005)** lung cancer cases in Saudia Arabia in the period between (2002-2003) are 183 cases in men and 60 cases in women , represent 9.5%of all other malignancies.

In 2007 , there was a report published by **Galal Fakkar** in Arab news about incidence of lung cancer among Saudis and mentioned that more than 250 people are diagnosed with lung cancer in Saudi Arabia 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. The increase coincided with a trend across the Kingdom for coffee shops tha5t cater exclusively serving women.

Al-Lawati et al .(1999) mentioned that the Cancer Oman National Registry collects data on all cancer cases occurring in Oman depending on population based registry in the period from January 1993 to December 1997. They reported 4091 cases of cancer (2282 males and 1809 females) . Lung cancer cases were 146 male cases , represented 6.4% of all other male malignant cases and among females , lung cancer cases were 52 cases , represented 2.9% of all other malignant female cases .

Young (2003) stated that in Jordan ,lung cancer was the first frequent cancer among males in the period 1996-1998 represented 17% of all other malignancies.

According to **young(2003)** in the period from 1996-1998 lung cancer cases in males represented 38% of all other cancer cases in Bahrain . While , in Qatar the percentage was 15% and in Emirates it was 8% of all other male cancer cases .

According to **Parkin et al. (2005)** in the period 2002-2003, there was high frequency of lung cancer in Kuwait and Palestine accounting for 14% and 15% respectively .

El-Bolkainy et al .(2005) mentioned that there were a study performed in Egypt on two pathology series of patients included 13.000 patients (El-Bolkainy) and 11.614 patients of National Cancer Institute (NCI) series from 1990 to 1997 of solid malignant tumors This study stated that , lung cancer represented 2.26% of all other malignancies . in El-Bolkainy private series and 1.48% of NCI cancer cases . In addition , lung cancer represented 3.4% of all new male cancer cases and 0.8% of all new female cancer cases .

According to **Gharbiah Population-based Cancer Registry (GPCR) in 1999 in Tanta Cancer Center** , total cancer cases were 3427 (1375 males and 1692 females) . Lung cancer cases were 182 cases per 100.000 population . Male lung cancer cases were 142 cases , represented 8.1% of all other malignancies as 8 out of every 10 patients with lung cancer were males . While, female cases were40 cases , represented 2.7% of all other malignancies . In addition , large cell carcinoma represented 19% , squamous cell carcinoma was 17% , adenocarcinoma represented 7% , anaplastic carcinoma 11% , small cell carcinoma was 6% and undefined malignancy was 40%.

Mokhtar et al ..(2007) reported that during the years 2003-2004 , the surgical Pathology Unit of department of pathology at Egyptian National Cancer Institute (NCI) has received 9808 cases of primary malignant solid tumors , represented 42% of all received cases through this period .Whereas primary malignant tumors of the respiratory system were the fifth most common tumors (578cases) in this registry material , constituted 5.90% of total malignancy , with high male predominance of 73% .Malignant lung tumors were 151 cases , represented 24.16% of tumors of the respiratory system and 1.54% of total malignant tumors . In addition , the undifferentiated large cell carcinoma represented 29.8% of malignant lung tumors . While squamous cell carcinoma was 21.8% of cases , adenocarcinoma represented 21.2% , undifferentiated small cell carcinoma was 15.2% of cases , mucoepidermoid carcinoma represented 3.3% , carcinoid tumors were 1.3% of cases and carcinoma in situ represented 0.6% of cases .

In 2006 lung cancer cases were 47.000, represented 0.06% of the total Egyptian population **(Govindan et al ., 2008).**

Age and sex :

Strand et al .(2007) mentioned that lung cancer is the leading cause of cancer-related death with an average five year survival rate of 15% of cases .

In 2006, lung cancer caused over 158,000 deaths worldwide (97.000 males and 61.000 females) more than colorectal, breast, and prostate cancers combined . Although death rates begin to decline among men, the lung recently surpassed the breast as the most common origin of fatal cancer in women . Several recent epidemiological studies in the last 20 years have indicated that female smokers may be more susceptible to lung cancer than male smokers **(Vineis et al ., 2007) .**

Levels of many hormones are powerful regulators of gene expression . Important elements in lung carcinogenesis may be hormonal regulation of genes involved in the metabolism of tobacco carcinogens and DNA repair . Interactions of smoking and hormonal status result in changes in the stroma and epithelial cells during tumor development **(Yin et al .,2007).**

Janssen-Heijnen and Coebergh (2008) stated that in UK lung cancer is rarely diagnosed in people younger than 40, but incidence rises steeply peaking in people aged 75-84 years . Most cases (85%) occur in people over the age of 60. 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 in 2004 was 7:5 (22,000 male cases and 15,000 female cases). Overall, 13% of all new cases of cancer are lung cancers.

Gharbiah Population-based Cancer Registry (GPCR) in 1999 in Tanta Cancer Center reported that the main age of male cancer cases was 65-69 years old . While , the main age of female lung cancer cases was 70-75 years old. Lung cancer intimately related to the spreading smoking epidemic in Egypt , occupies the fourth rank after non-Hodgkin lymphoma.

Mokhtar et al .(2007) mentioned that , in Egyptian National Cancer Institute (NCI) , in the period from 2003-2004 , the respiratory malignant tumors in males were 422 cases , represented 8.7% of all male malignant tumors .However , for females , the respiratory malignant tumors were 156 cases which represented 3.1% of all female malignant tumor cases .

Dubey and Powell (2007) reported that lung cancer occurs most often between ages 40 and 70 years , with a peak incidence in the fifties or sixties . Only 2% of all cases appear before the age of 40 . Furthermore , the histological pattern of lung cancer changed over time as squamous cell carcinoma is the most common type among men , while adenocarcinoma is the most frequent type among women .

According to **Mokhtar et al .(2007)** in the same study of Egyptian NCI in the period from 2003-2004 , the adult cases represented 98.5% of the respiratory malignant tumors and the pediatric cases represented 1.38% of cases .

Race and Ethnicity:

Esteve et al .(2005) stated that The patterns of occurrence of lung cancer by race and ethnicity make lung cancer a relevant disease for those concerned with the health of women and minorities. Whereas lung cancer incidence rates are similar among African-American and white women, lung cancer occurs about 50% more frequently among African-American men than among white men. The marked reduction in cigarette smoking that has occurred among African-American youths forecasts a possible reversal of this trend, and, if this trend persists, declines in the incidence of lung cancer among African-Americans can be expected. Other ethnic groups such as Hispanics and Asians have lower rates than whites

Within the UK, south Asians have a lower incidence of lung cancer than non-south Asians. but increasing incidence has been reported amongst south Asian men, in contrast to the rest of the UK male population. South Asian women also have increasing lung cancer trends but this is in line with the rest of the UK female population **(Smith ,2006).**

***Geographic patterns* :**

The poor prognosis for lung cancer means that incidence and mortality patterns are very similar in all parts of the world. Lung cancer is the most commonly diagnosed cancer worldwide , but its geographic distribution shows marked regional variation . 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 . It accounts for 22% versus 14.6% of cancer deaths , respectively. Within Europe the countries with the highest male rates are Hungary and Poland and the lowest in Sweden and Malta . For women the highest rates of lung cancer are found in northern America and northern Europe. Women in the USA have the world's highest lung cancer incidence rates followed by Canada. The lowest lung cancer incidence rates in both men and women are found in African and Asian countries. However , the lung cancer epidemic begins to subside in the developed countries, it is on the rise in the developing world **(Travis et al ., 2004).**

Morbidity /Mortality :

Peto et al .(2006) mentioned that lung cancer has an enormous impact on national mortality. As it is the cause of 1 million deaths each year worldwide, accounting for 6% of all deaths and 22% of all deaths from cancer. In the United States ,the 5-year survival rate represent 14% of patients , while in Europe , the 5-year overall survival rate is 8% , similar to that of the developing world .

Dunham (2008) reported that in 2007 , About 7.6 million people worldwide died from various types of cancer and lung cancer heavily driven by smoking , killed 975,000 men and 376,000 women .

Swerdlow et al .(2006) stated that in 2005 there were around 243,100 lung cancer deaths each year in the European Union (around 188,000 in men and 55,000 in women). As in the UK lung cancer was responsible for nearly a quarter (24%) of all male cancer deaths and nearly a fifth (19%) of all female cancer deaths . Furthermore , the ages at which people die from lung cancer, three-quarters 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.

In the United States, deaths from lung cancer have decreased significantly by 2.0% per year from 1994 to 2004 among men and increased significantly by 0.2% per year from 1995 to 2004 among women . However , the number one cause of cancer death in the United States is cancer of the lung and bronchus. Even when analyzed by race and sex, lung cancer is number one for white males and females and for black males. For black females, breast cancer mortality is slightly higher than lung cancer **(Brennan and Bray,2005)**

Ries et al.(2007) reported that in 2000 , Lung cancer caused 4,594 deaths in men in Australia , accounted for 22.9% of male cancer deaths .

Risk factors and Pathogenesis :

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

1-Tobacco smoking :

Grannis (2007) stated that smoking is by far the leading risk factor for lung cancer. About 87% of all lung cancer deaths are thought to result from smoking or passive exposure to tobacco smoke . Risk of developing lung cancer is affected by level of consumption and duration of smoking. 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 far more dependent on duration of smoking than consumption: smoking one pack of cigarettes a day for 20 years may be as much as 16 times more hazardous than smoking one pack a day for 10 years. There is also evidence that starting to smoke at a young age carries additional risks of lung damage.

The mortality rate ratio for lung cancer in smokers versus nonsmokers was 14:9 and this dropped to 4:1 in ex-smokers **(Taylor et al .,2007)**

Vineis et al.(2005) mentioned that 10 years after stopping smoking , the risk is reduced to one-third of what it would have been present with continuous smoking . A lifelong male smoker has a cumulative risk of 15.9% for developing lung cancer by age 75. For men who cease smoking at ages 60, 50, 40 and 30 years, their cumulative risk of dying from lung cancer falls to 9.9%, 6.0%, 3.0% and 1.7% respectively. Smoking cessation has the same health benefits for women with the cumulative risk of dying from lung cancer up to age 75 being 9.5% for life-long smokers, and falling to 5.3% and 2.2% for women who stopped smoking around age 60 and 50 respectively.

Taylor et al .(2007) stated that there were studies in Europe and China reported that exposure to Environmental Tobacco Smoke (ETS) at work may increase the risk of lung cancer by 65–80%. Exposure to ETS at home during childhood carries even higher risks, while non-smoking adults who live with smokers have been shown to have a 27% increased risk of developing lung cancer. Also cigar smoking and pipe smoking are almost as likely to cause lung cancer as cigarette smoking.

Wen et al .(2006) mentioned that , whereas SCLC has persisted at approximately 20% in most series, adenocarcinoma has increased to 45% with declines in squamous cell and large cell carcinoma. They have suggested that these changes are the results of cigarette design, e.g., the smoke in filter tip cigarettes is inhaled more deeply than earlier,

unfiltered cigarettes (more toxic), and deeper inhalation transports tobacco-specific carcinogens more distally toward the bronchoalveolar junction where adenocarcinomas often arise . In addition, blended reconstituted tobacco includes more stems than leaves which release higher concentrations of *N*-nitrosamines as among the more than 60 carcinogens in tobacco and cigarette smoke, the two major classes are polycyclic aromatic hydrocarbons and nitrosamines.

2-Hookah smoking :

Hookah smoking has become popular among young people in recent years. It is often marketed as being safer than cigarettes because the percentage of tobacco in the product smoked is low and the smoke is filtered through water. But it is not true that hookah smoking is safe. Studies have shown that hookah smoke contains the same cancer-causing substances as cigarettes (**Gray , 2003).**

3- Radon :

According to **Darby et al.(2005)** radon is a known human carcinogen and increased risks of lung cancer were first observed in uranium miners with high radon exposure levels. It is a naturally occurring radioactive gas that forms from the breakdown of uranium in soil and rocks. It cannot be seen, tasted, or smelled. According to the U.S. Environmental Protection Agency (EPA), radon is the second leading cause of lung cancer, and is the leading cause among nonsmokers. Outdoors, there is so little radon that it is not dangerous. But indoors, radon can be more concentrated and become a possible risk for cancer. Radon can also accumulate in homes and other buildings at much lower levels. As indoor radon exposure is responsible for 9% of lung cancers in European countries.

Exposure to radon multiplies the risk of lung cancer for both smokers and non-smokers by the same amount but its effect is much greater for smokers as their risk of lung cancer is already much higher.The absolute risk of lung cancer by age 75 among non-smokers was an estimated 0.93%, while for smokers it was 21.6% **(Field et al .,2006).**