Epidemiology, pathogenesis, and risk factors

US Incidence and mortality

Lung cancer is the leading cause of cancer-related death in both genders worldwide, expected to account for 224,210 new cases and 159,260 deaths in the USA, for the year 2014.

It is the second most common solid tumour type in both genders, after prostate cancer in men and breast cancer in women.

Lung cancer is the cause of 28% and 26% of all male and female cancer-related deaths, respectively, exceeding prostate and breast cancer mortality.

Lung cancer US incidence rates in both genders have been increasing from the 1970s, until the mid 1980s in men and the late 1990s in women.

Incidence is now beginning to decline, possibly as a consequence of a reduced smoking prevalence. Differences in lung cancer incidence patterns between men and women reflect mainly historical disparities in smoking habits.

Cigarette smoking prevalence peaked about 20 years later in women than in men.

US lung cancer death rates rose for most of the 20th century, peaking at the beginning of the 1990s for men and almost two decades later for women.

Lung cancer death rates have followed the same trend as smoking prevalence and incidence rates, demonstrating the strong correlation between the major risk factor and the disease and the poor prognosis of this malignancy, respectively.

Recently, a steady decline in lung cancer death rates has been described in both sexes, as a result of combined improvements in primary prevention, control of associated risk factors, and treatment.

REVISION QUESTIONS

1. What is the trend of lung cancer incidence in the USA in the last 15 years?
2. Is there a difference in lung cancer mortality rates between men and women?
3. What is the percentage of deaths due to lung cancer among all cancer-related deaths?
European scenario

European predictions for the year 2014 in men and women, respectively, estimate over 187,000 (25% of all cases) and 84,000 lung cancer-related deaths.

Lung cancer is the primary cause of cancer-related deaths for men in Europe, being second only to breast cancer for women.

European mortality for lung cancer peaked in the late 1980s for men and began declining later, while, for women, differently to the US scenario, mortality continues to increase with a prediction of 14.1 cases/100,000 in 2014. An opposite trend has been observed for breast cancer.

An evaluation performed in 2012 revealed that the lung cancer incidence rate for men was highest in Central and Eastern European countries and lowest in Northern Europe.

On the contrary, the incidence rate for women was highest in Northern European countries and lowest in Eastern Europe.

For both sexes combined, the lowest rates were seen in Cyprus and the highest in Hungary, with a range varying from 49 to 156 cases/100,000.

The lung cancer rate in underdeveloped countries is lower than in developed ones, although incidence and mortality are slowly increasing.

The World Health Organisation estimates that lung cancer deaths worldwide will continue to rise, largely as a result of an increase in global tobacco use.

Worldwide, every year, as many people die from lung cancer as the cumulative number resulting from prostate, breast, and colon cancers.

REVISION QUESTIONS
1. Are there differences in lung cancer mortality rates between the USA and Europe?
2. Is lung cancer incidence homogeneous throughout Europe?
3. What is the mortality rate due to lung cancer compared with other “big killers”?
Clinical features and survival expectancy

Only 15% of all lung cancer cases is diagnosed at an early stage, with a 5-year survival rate higher than 50%.

In a large percentage of cases, lung cancer is diagnosed at an advanced stage with distant metastases and a 5-year survival rate of about 4%.

Five-year survival rate for all lung cancer stages combined is about 17%.

Lung cancer in both sexes is predominantly diagnosed in the elderly population (median age at diagnosis is 71 years).

Compared with men, women are less likely to have a smoking history, are generally younger at the time of diagnosis, and have a better survival expectancy at any stage, independent of the therapeutic approach.

Adenocarcinoma of the lung is the most common histological subtype among women.

Adenocarcinoma accounts for 38.5% of all lung cancer cases, while squamous cell carcinoma and large cell carcinoma account for 20.0% and 2.9%, respectively.

In the past decades, adenocarcinoma incidence has progressively increased, and nowadays it has replaced squamous cell carcinoma as the most prevalent histotype of non-small cell lung cancer.

Adenocarcinoma of the lung is also the most represented histotype among never-smokers.

REVISION QUESTIONS
1. What is the proportion of patients with lung cancer diagnosed at early stage of disease?
2. Is there a correlation between a clinical characteristic (such as female gender or smoking attitude) and one specific histotype?
3. Is the subtype histology prevalence the same compared with 30 years ago?
Pathogenesis of lung cancer

The major function of the lungs is respiratory exchange: inhaled air and potentially dangerous substances are conducted to the alveoli through a network of bronchi and bronchioles.

The putative stem cells of the bronchus are the basal cells, which are believed to give rise to the differentiation of ciliated, mucous, and neuroendocrine cells.

Lung cancer may arise from all these differentiated and undifferentiated cells, from either the central (small cell lung cancer and squamous cell carcinoma) or the peripheral (adenocarcinoma) airway compartment.

The interaction between inhaled carcinogens and the epithelium of upper and lower airways leads to the formation of DNA adducts: pieces of DNA covalently bound to a cancer-causing chemical.

Repair processes may remove the DNA adducts and restore normal DNA, or alternatively cells with damaged DNA may undergo apoptosis.

If DNA adducts persist or are misrepaired, they result in a mutation and can cause genomic alterations, key events in lung cancer pathogenesis, especially if they occur in critical oncogenes and tumour suppressor genes.

Lung cancer pathogenesis is also affected by a genetic component: it relates to the host susceptibility to lung cancer, with or without exposure to certain carcinogens.

Studies on familial aggregation have supported the hypothesis that a multifactorial hereditary component is possible for this disease, even if a clear mechanism of familial transmission is still not described.

The addition of smoking to this genetic inheritance is associated with a 3-fold increased risk of lung cancer.

REVISION QUESTIONS
1. Is there a unique and specific component of airway epithelium from which lung cancer can arise?
2. What are the consequences of the action of inhaled carcinogens on the airways’ epithelium?
3. Does the hereditary component have a role in lung cancer pathogenesis?
Risk factors

Smoking is considered the principal risk factor for lung cancer, causing more than 80% of all cases.

Non-smoking-related risk factors include occupational exposure to asbestos, chromium, arsenic, cadmium, silica, and nickel, as well as second-hand smoke, outdoor air pollutants, previous lung diseases, radon exposure, and dietary factors.

In the absence of such risk factors, the genetic susceptibility to lung cancer remains the only other parameter predisposing to the onset of the disease.

An estimated 10–25% of lung cancers worldwide occur in never-smokers, defined as individuals who have smoked less than 100 cigarettes in their lifetime.

Cancers arising in never-smokers predominantly target the distal airways, favouring adenocarcinoma histology and female gender. One of the most relevant risk factors is environmental tobacco smoke exposure.

Lung cancer prevalence in never-smokers is higher in Asian countries, especially in women, probably due to the inhalation of cooking oil vapours and particles emitted by domestic use of coal for cooking and heating.

The relative risk of lung cancer in long-term smokers has been estimated as 10- to 30-fold higher compared with non-smokers.

The International Agency for Research on Cancer (IARC) has identified at least 50 carcinogens in tobacco smoke, targeting both central and peripheral airways.

The most potent carcinogens of cigarette smoke are the polycyclic aromatic hydrocarbons (PAHs) and the aromatic amines, N-nitrosamines, but it also contains benzene, vinyl chloride, arsenic, chromium, radon, and its decay products, bismuth and polonium.

REVISION QUESTIONS
1. What is the definition of “never-smokers”?
2. Is there a different distribution of lung cancer in never-smokers across the world?
3. Which are the most potent carcinogens of cigarette smoke?
Summary: Epidemiology, pathogenesis, and risk factors

- Lung cancer is the leading cause of cancer-related death worldwide in both genders, surpassing prostate and breast cancer mortality
- US incidence rates in both genders increased until the 1990s and began to decline later, similar to the trend in mortality
- In Europe, lung cancer-related deaths for women are secondary only to breast cancer and, differently to the US scenario, the mortality rate continues to increase
- Worldwide, every year, as many people die from lung cancer as from the other “big killers” (prostate, breast, and colon cancer) combined together
- Only 15% of all lung cancer cases are diagnosed at an early stage, while the majority present with distant metastases at diagnosis with a 5-year survival rate of about 4%
- Median age at diagnosis is 71 years and adenocarcinoma is nowadays the most prevalent histotype
- Lung cancer may arise from all the differentiated and undifferentiated cells of the upper and lower airways, and the formation of DNA adducts as a consequence of the inhalation of carcinogens plays a central role in lung cancer pathogenesis
- Lung cancer pathogenesis is also affected by a genetic multifactorial susceptibility, which may be further influenced by exposure to certain carcinogens
- Smoking is the principal risk factor for lung cancer: long-term smokers have a 10- to 30-fold higher risk compared with non-smokers
- Non-smoking-related risk factors include occupational exposure to carcinogens, second-hand smoke, pollution, dietary factors, radon exposure, and genetic susceptibility to cancer

Further Reading


