



# Lung Cancer

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## DEFINITION AND EPIDEMIOLOGY

Lung cancer is the second most common cancer in both women and men; however, it is the leading cause of cancer death in both genders in the United States, and an estimated 1 million people die worldwide of lung cancer each year. Despite recent advances in understanding of the biology and genetics of lung cancer and the advent of novel therapeutic agents for its treatment, the 5-year survival rate for patients with lung cancer is only about 15%. The relatively poor rate of long-term survival partly stems from the fact that most patients with lung cancer have an advanced stage of the disease at the time of diagnosis.

There are two major types of bronchogenic carcinoma: *small cell carcinoma* (SCLC) (E-Fig. 56-1) and *non-small cell carcinoma* (NSCLC). NSCLCs are more common and include adenocarcinoma (32%) (E-Fig. 56-2), squamous cell carcinoma (30%) (E-Fig. 56-3), large cell carcinoma (10%) (E-Fig. 56-4), and some more poorly differentiated histologic subtypes not otherwise specified (NOS). SCLCs account for fewer than 20% of all bronchogenic carcinomas.

A current or prior cigarette smoking history remains the leading known risk factor for the development of lung cancer, although up to 15% of newly diagnosed NSCLC cases, often of the adenocarcinoma subtype, are seen in nonsmokers. It has been estimated that 1 in 5 adults is a current everyday cigarette smoker, implying that lung cancer will continue to be a major public health burden in the coming decades. SCLC is predominantly correlated with cigarette smoking, which plays a key pathogenic role in the disease, whereas NSCLC is commonly diagnosed in never-smokers or in those with only a light-smoking history. In recent years, it has been recognized that lung cancer in smokers is a different disease from lung cancer in nonsmokers at both the molecular and the genetic/genomic levels.

The risk for lung cancer is generally proportionate to number of cigarette pack-years smoked (packs per day  $\times$  years smoked), and the incidence peaks in the sixth and seventh decades. Ex-smokers show a persistent risk for lung cancer throughout life. Passive smoking also contributes as a cause of lung cancer in a portion of nonsmokers who develop the disease. Nonsmokers who live with smokers have a more than 30% increased risk of developing lung cancer. Other risk factors for lung cancer include environmental hazards such as asbestos and petroleum exposure. Smoking is considered an important cofactor of lung cancer in the setting of asbestos exposure. Radon exposure also increases the risk for lung cancer (see Chapter 54).

Understanding of the underlying pathogenic mechanisms of lung cancer has evolved to recognize the disease as a genetic

or even genomic disease. An ever-growing list of oncogenic alterations identified in both proto-oncogenes and tumor suppressor genes is accumulating as a result of the genomic analysis effort in recent years, including The Cancer Genome Atlas (TCGA) project sponsored by the National Institutes of Health (NIH) in the United States (see later discussion).

Unique molecular-genomic subgroups of lung cancer have been recognized, including those harboring (1) mutated epidermal growth factor receptor (*EGFR/ERBB1*), (2) mutated Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and (3) anaplastic lymphoma kinase (*ALK*) 2p23 chromosomal rearrangement, more commonly as *EML4-ALK*, a fusion with echinoderm microtubule-associated protein-like 4 (*EML4*). Importantly, these oncogenic genomic alterations provide therapeutic windows of opportunity, especially in the context of oncogenic addiction resulting from these alterations in the tumor cells.

Several targeted therapies have been approved by the U.S. Food and Drug Administration (FDA) for treatment of advanced NSCLCs containing mutated *EGFR* (erlotinib, afatinib, and gefitinib) or the *ALK* 2p23 rearrangement (crizotinib). Lung cancers with *EGFR* mutations are more frequently identified in never-smokers or in those with a light-smoking history, are more often of the adenocarcinoma subtype, and are more often, but not exclusively, diagnosed in females and in patients of East Asian ethnicity. *KRAS*-mutated lung cancers are found primarily in patients with heavier smoking exposure. Lung cancers with mutated *EGFR* and those with the *ALK* 2p23 rearrangement are typically seen in younger patient populations, with the median age at diagnosis being approximately 55 years.

## PATHOLOGY

### Histologic Subgroups

#### Non-Small Cell Lung Carcinomas

Most lung cancers fall under the major histologic subgroup of NSCLCs. Of these, *adenocarcinomas* and *squamous cell carcinomas* are the most common.

#### Adenocarcinomas

Adenocarcinoma is the most commonly diagnosed subtype of lung cancer, accounting for approximately 40% of lung cancer diagnoses and 65,000 deaths each year in the United States. It is the histologic subtype most commonly diagnosed in nonsmokers. Primary lung adenocarcinomas are usually found in the periphery of the lung (75%) (E-Fig. 56-5), in contrast to squamous cell carcinomas.