willing to work hard to achieve the goal of smoking abstinence. Self-help strategies alone only marginally affect quit rates, whereas individual and combined pharmacotherapies in combination with counseling can significantly increase rates of cessation. Therapy with an antidepressant (e.g., bupropion) and nicotine replacement therapy (varenicline, a $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist) are approved by the U.S. Food and Drug Administration (FDA) as first-line treatments for nicotine dependence. However, both drugs have been reported to increase suicidal ideation and must be used with caution. In a randomized trial, varenicline was shown to be more efficacious than bupropion or placebo. Prolonged use of varenicline beyond the initial induction phase proved useful in maintaining smoking abstinence. Clonidine and nortriptyline are recommended as second-line treatments. Of note, reducing cigarettes smoked before quit day and quitting abruptly, with no prior reduction, yield comparable quit rates. Therefore, patients can be given the choice to quit in either of these ways (Chap. 470).

**Inherited Predisposition to Lung Cancer** Exposure to environmental carcinogens, such as those found in tobacco smoke, induce or facilitate the transformation from bronchoepithelial cells to the malignant phenotype. The contribution of carcinogens on transformation is modulated by polymorphic variations in genes that affect aspects of carcinogen metabolism. Certain genetic polymorphisms of the P450 enzyme system, specifically CYP1A1, and chromosome fragility are associated with the development of lung cancer. These genetic variations occur at relatively high frequency in the population, but their contribution to an individual's lung cancer risk is generally low. However, because of their population frequency, the overall impact on lung cancer risk could be high. In addition, environmental factors, as modified by inherited modulators, likely affect specific genes by deregulating important pathways to enable the cancer phenotype.

First-degree relatives of lung cancer probands have a two- to threefold excess risk of lung cancer and other cancers, many of which are not smoking-related. These data suggest that specific genes and/or genetic variants may contribute to susceptibility to lung cancer. However, very few such genes have yet been identified. Individuals with inherited mutations in *RB* (patients with retinoblastoma living to adulthood) and *p53* (Li-Fraumeni syndrome) genes may develop lung cancer. Common gene variants involved in lung cancer have been recently identified through large, collaborative, genome-wide association studies. These studies identified three separate loci that are associated with lung cancer (5p15, 6p21, and 15q25) and include genes that regulate acetylcholine nicotinic receptors and telomerase production. A rare germline mutation (T790M) involving the epidermal growth factor receptor (EGFR) maybe be linked to lung cancer susceptibility in never smokers. Likewise, a susceptibility locus on chromosome 6q greatly increases risk lung cancer risk among light and never smokers. Although progress has been made, there is a significant amount of work that remains to be done in identifying heritable risk factors for lung cancer. Currently no molecular criteria are suitable to select patients for more intense screening programs or for specific chemopreventative strategies.

## PATHOLOGY

The World Health Organization (WHO) defines lung cancer as tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). The WHO classification system divides epithelial lung cancers into four major cell types: small-cell lung cancer (SCLC), adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma; the latter three types are collectively known as non-small-cell carcinomas (NSCLCs) (Fig. 107-1). Small-cell carcinomas consist of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, absent or inconspicuous nucleoli, and a high mitotic count. SCLC may be distinguished from NSCLC by the presence of neuroendocrine markers including CD56, neural cell adhesion molecule (NCAM), synaptophysin, and chromogranin. In North America, adenocarcinoma is the most common histologic type of lung cancer. Adenocarcinomas possess glandular differentiation or mucin production and may show acinar, papillary, lepidic, or solid features or a mixture of these patterns. Squamous cell carcinomas of the lung are morphologically identical to extrapulmonary squamous cell carcinomas and cannot be distinguished by immunohistochemistry alone. Squamous cell tumors show keratinization and/or intercellular bridges that arise from bronchial epithelium. The tumor tends to consists of sheets of cells rather than the three-dimensional groups of cells characteristic of adenocarcinomas. Large-cell carcinomas comprise less than 10% of lung carcinomas. These tumors lack the cytologic and architectural features of small-cell carcinoma and glandular or squamous differentiation. Together these four histologic types account for approximately 90% of all epithelial lung cancers.

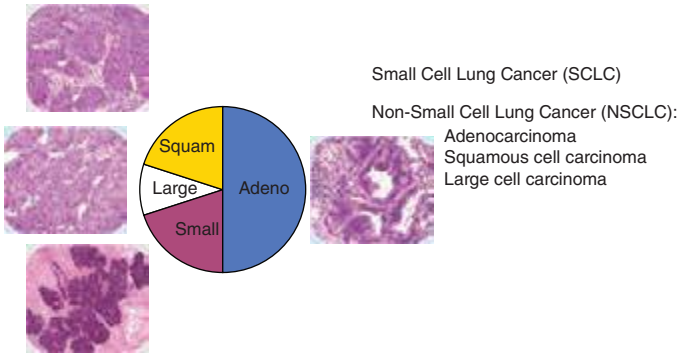


**FIGURE 107-1** **Traditional histologic view** of lung cancer.

All histologic types of lung cancer can develop in current and former smokers, although squamous and small-cell carcinomas are most commonly associated with heavy tobacco use. Through the first half of the twentieth century, squamous carcinoma was the most common subtype of NSCLC diagnosed in the United States. However, with the decline in cigarette consumption over the past four decades, adenocarcinoma has become the most frequent histologic subtype of lung cancer in the United States as both squamous carcinoma and small-cell carcinoma are on the decline. In lifetime never smokers or former light smokers (<10 pack-year history), women, and younger adults (<60 years), adenocarcinoma tends to be the most common form of lung cancer.

Historically, the major pathologic distinction was simply between SCLC and NSCLC, because these tumors have quite different natural histories and therapeutic approaches (see below). Likewise, until fairly recently, there was no apparent need to distinguish among the various subtypes of NSCLC because there were no clear differences in therapeutic outcome based on histology alone. However, this perspective radically changed in 2004 with the recognition that a small percentage of lung adenocarcinomas harbored mutation in *EGFR* that rendered those tumors exquisitely sensitive to inhibitors of the EGFR tyrosine kinases (e.g., gefitinib and erlotinib). This observation, coupled with the subsequent identification of other "actionable" molecular alterations (Table 107-1) and the recognition that some active

**TABLE 107-1 DRIVER MUTATIONS IN NON-SMALL-CELL LUNG CANCER (NSCLC)**

| Gene | Alteration | Frequency in NSCLC | Typical Histology |
|---|---|---|---|
| *AKT1* | Mutation | 1% | Adenocarcinoma, squamous |
| *ALK* | Rearrangement | 3–7% | Adenocarcinoma |
| *BRAF* | Mutation | 1–3% | Adenocarcinoma |
| *DDR2* | Mutation | ~4% | Squamous |
| *EGFR* | Mutation | 10–35% | Adenocarcinoma |
| *FGFR1* | Amplification | ~20% | Squamous |
| *HER2* | Mutation | 2–4% | Adenocarcinoma |
| *KRAS* | Mutation | 15–25% | Adenocarcinoma |
| *MEK1* | Mutation | 1% | Adenocarcinoma |
| *MET* | Amplification | 2–4% | Adenocarcinoma |
| *NRAS* | Mutation | 1% | Adenocarcinoma |
| *PIK3CA* | Mutation | 1–3% | Squamous |
| *PTEN* | Mutation | 4–8% | Squamous |