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**Chapter Overview**

Lung cancer development is thought to involve a multistep tumorigenesis process occurring in a field of carcinogenic exposure. The molecular events associated with lung cancer development involve genetic and epigenetic changes involving oncogenes, tumor suppressor genes, and regulatory genes that affect basic cellular processes, including growth, immortalization (escape from senescence), evasion from cell death, sustained angiogenesis, and the ability to take over the epithelium, invade, and metastasize. The process of lung cancer development is augmented by molecular changes that enhance genomic instability, especially in the setting of chronic exposure of the lung to carcinogens. Knowledge of the lung tumorigenesis pathway and direct measurement of these changes in lung tissue provide the opportunity to assess the risk of cancer in individuals exposed to carcinogens such as tobacco smoke, to directly examine the impact of chemopreventive treatments on the lungs, to aid in early detection, to assess prognosis in patients with established lung cancer, and potentially to identify the most appropriate treatment approach for an individual’s tumor. Knowledge of the molecular attributes of lung tumors also provides the opportunity to develop therapies directly targeted to correcting defective cellular pathways, either through inhibition of dysregulated signaling or through replacement of defective genes. Molecular therapeutic approaches are now being used in the preventive setting as well as in the therapeutic setting in combination with surgery, radiation therapy, and chemotherapy.

**Introduction**

Lung cancer remains a major challenge in the world. Despite improvements in staging and the application and integration of surgery, radiation therapy, and chemotherapy, the 5-year survival rate for individuals with lung cancer remains around 15%. One reason for this low survival rate is that many lung cancers are detected at an advanced stage and thus are difficult to manage. Another reason for the low survival rate is the high frequency of second primary tumors in individuals definitively treated for a first primary lung tumor (i.e., about 2% per year in patients with non–small cell lung cancer and 4% to 6% per year in patients with small cell lung cancer). Progress toward decreasing the morbidity of lung cancer will depend on the development of new strategies for prevention, early detection, and treatment that are tailored specifically for this disease. The development of new strategies in turn will depend on a better understanding of the etiology and biology of lung cancer development and its response to intervention. Once this understanding is achieved, new strate-