tobacco smoking. The molecular changes to vary among the histologic subtypes, which will be described later. Suffice it to say that lung cancers can be broadly classified into small cell and non-small cell types and the latter group is made up of squamous cell and adenocarcinomas.

Tobacco Smoking. **About 80% of lung cancers occur in active smokers or those who stopped recently.** There is a nearly linear correlation between the frequency of lung cancer and pack-years of cigarette smoking. The increased risk becomes 60 times greater among habitual heavy smokers (two packs a day for 20 years) compared with nonsmokers. However, since lung cancer develops in only 11% of heavy smokers, there are other factors that predispose individuals to this deadly disease. For reasons not entirely clear, women have a higher susceptibility to carcinogens in tobacco than men. Although cessation of smoking decreases the risk for lung cancer over time, it may never return to baseline levels. In fact, genetic changes that predate lung cancer can persist for many years in the bronchial epithelium of former smokers. Passive smoking (proximity to cigarette smokers) increases the risk for lung cancer development to approximately twice that of nonsmokers. The smoking of pipes and cigars also increases the risk, but only modestly.

Although the duration and intensity of smoking are well correlated with cancer risk, not all persons exposed to tobacco smoke develop cancer. Some of this may be a matter of chance, but it is also likely that the mutagenic effect of carcinogens in smoke is modified by genetic variants. Recall that many chemicals (procarcinogens) are converted into carcinogens via activation by the highly polymorphic P-450 monooxygenase enzyme system (Chapter 9). Specific P-450 polymorphisms have an increased capacity to activate procarcinogens in cigarette smoke, and smokers with these genetic variants appear to incur a greater risk of lung cancer. Similarly, individuals whose peripheral blood lymphocytes show more numerous chromosomal breakages after exposure to tobacco-related carcinogens (mutagen sensitivity genotype) have a greater than 10-fold higher risk of developing lung cancer as compared with controls, presumably because of genetic variation in genes involved in DNA repair.

The histologic changes that correlate with steps along the path to neoplastic transformation are best documented for squamous cell carcinomas and are described in more detail later. There is a linear correlation between the intensity of exposure to cigarette smoke and the appearance of ever more worrisome epithelial changes. These begin with rather innocuous-appearing basal cell hyperplasia and squamous metaplasia and progress to squamous dysplasia and carcinoma in situ, the last stage before progression to invasive cancer.

Unfortunately, the carcinogenic effects of tobacco smoke extend to those who live and work with smokers. *Secondhand smoke*, or environmental tobacco smoke, contains numerous human carcinogens for which there is no safe level of exposure. It is estimated that each year about 3000 nonsmoking adults die of lung cancer as a result of breathing secondhand smoke. Cigar and pipe smoking also increase risk, although much less than smoking cigarettes. Smokeless tobacco is not a safe substitute for smoking cigarettes or cigars, as these products spare the lung but cause oral cancers and can lead to nicotine addiction.

Industrial Hazards. Certain industrial exposures, such as asbestos, arsenic, chromium, uranium, nickel, vinyl chloride and mustard gas, increase the risk of developing lung cancer. High-dose ionizing *radiation* is carcinogenic. There was an increased incidence of lung cancer among survivors of the Hiroshima and Nagasaki atomic bomb blasts, as well as in workers heavily involved in clean-up after the Chernobyl disaster. *Uranium* is weakly radioactive, but lung cancer rates among nonsmoking uranium miners are four times higher than those in the general population, and among smoking miners they are about 10 times higher. *Asbestos* exposure also increases the risk for lung cancer development. The latent period before the development of lung cancer is 10 to 30 years. Lung cancer is the most frequent malignancy in individuals exposed to asbestos, particularly when coupled with smoking. Asbestos workers who do not smoke have a five-fold greater risk of developing lung cancer than do nonsmoking control subjects, and those who smoke have a 55-fold greater risk.

Air Pollution. It is uncertain whether air pollution, by itself, increases the risk of lung cancer, but it likely adds to the risk in those who smoke or are exposed to secondhand smoke. It may do so through several different mechanisms. Chronic exposure to air particulates in smog may cause lung irritation, inflammation and repair, and you will recall that chronic inflammation and repair increases the risk of a variety of cancers (Chapter 7). A specific form of air pollution that may contribute to an increased risk of lung cancer is radon gas. Radon is a ubiquitous radioactive gas that has been linked epidemiologically to increased lung cancer in uranium miners, particularly those who smoke. This has generated concern that low-level exposure (e.g., in well-insulated homes in areas with naturally high levels of radon in soil) may also increase the incidence of lung cancers, but this point remains unsettled.

Molecular Genetics. As with other cancers (Chapter 7), smoking-related carcinomas of the lung arise by a stepwise accumulation of oncogenic "driver" mutations that result in the neoplastic transformation of pulmonary epithelial cells. Some of the genetic changes associated with cancers can be found in the "benign" bronchial epithelium of smokers without lung cancers, suggesting that large areas of the respiratory mucosa are mutagenized by exposure to carcinogens in tobacco smoke ("field effect"). On this fertile soil, those few cells that accumulate a sufficient panoply of complementary driver mutations to acquire all of the hallmarks of cancer (Chapter 7) develop into invasive carcinomas.

Lung carcinomas fall into several major histologic subgroups (described later), each with distinctive molecular features, as follows:

- *Squamous cell carcinoma* is highly associated with exposure to tobacco smoke and harbors diverse genetic aberrations, many of which are chromosome deletions involving tumor suppressor loci. These losses, especially those involving 3p, 9p (site of the *CDKN2A* gene), and 17p (site of the *TP53* gene) are early events in tumor evolution, being detected at an appreciable frequency in the histologically normal respiratory mucosal cells of smokers. Squamous cell carcinomas show the highest